PROTOCOL TITLE: Comparison of gabapentin and metoclopramide for treating hyperemesis gravidarum.

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## PROTOCOL TITLE:

*Include the full protocol title.*

Response: Comparison of gabapentin and metoclopramide for treating hyperemesis gravidarum.

## PRINCIPAL INVESTIGATOR:

*Name*
*Department*
*Telephone Number*
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## VERSION NUMBER:

*Include the version number of this protocol.*

Response: 9

## DATE:

*Include the date of submission or revision.*

Response: 5.2.16

## Grant Applicability:

*Describe whether or not this protocol is funded by a grant or contract and if so, what portions of the grant this study covers.*

Response: This study is being supported by the National Institute of Health (NIH)

## Table of Contents

# 1.0 Objectives

*1.1 Describe the purpose, specific aims, or objectives.*

Response:

Aim 1. To compare the efficacy and tolerability of gabapentin and metoclopramide in the treatment of HG.

Aim 2. (1) (Exploratory) To assess the change from Baseline in efficacy measures after 2 weeks of open-label gabapentin; and (2) (Descriptive) to assess the mean gabapentin dose, duration of gabapentin treatment and frequency of rescue metoclopramide pills required by patients during the entire open-label gabapentin phase of the study.

*1.2 State the hypotheses to be tested.*

Response: Is gabapentin more effective than metoclopramide for the treatment of nausea and vomiting in women with hyperemesis gravidarum?

# 2.0 Background

*2.1 Describe the relevant prior experience and gaps in current knowledge.*

*See section 2.3.*

*2.2 Describe any relevant preliminary data.*

Response: See description above in Section 2.3

*2.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.*

Response:

Hyperemesis gravidarum (HG) is a disease of severe nausea, vomiting, and anorexia associated with early pregnancy leading to dehydration and weight loss. HG has been coined a "heart-sink problem" for gynecologists because of the frustration of not being able to cure such distressed women and because of the prolonged and repeated hospital admissions.[1] A recent meta-analysis of HG randomized controlled trials concluded that there are no effective treatments for this condition.[2] As a result, more than 50,000 HG patients a year require hospital admission for intravenous (iv) hydration or parenteral nutrition.[3,4] It is estimated that about 206 hours of paid work are lost for each woman with nausea and vomiting of pregnancy.[5]

HG also inflicts significant psychosocial burden on patients. In a recent on-line survey of 808 women with HG, 15.2% reported electively terminating at least one pregnancy due to HG.[6] The top 3 reasons for terminating were "No hope for relief" (87.0%), "Unable to care for self or family" (66.7%), and "Emotional distress" (60.2%). In this same survey, an additional 12.7% of women with HG reported that they "almost" terminated a pregnancy due to HG. Therefore, about 28% of babies whose mothers have

HG are at high risk for death. There is a large clinical need for a safe and effective treatment for HG that will bring meaningful benefit and, consequently, decrease the high rate of associated fetal mortality.

Eight of the 9 published HG randomized controlled trials (RCTs) have assessed their primary outcome measures while subjects were inpatients, where subjects experience very high placebo effects especially regarding rates of emesis (placebo effect mean of 82%).[1,7-13] Even though patients' symptoms improve greatly when they are inpatients, about 35% require readmission after discharge.[14] It is this phenomenon of symptom recurrence in the outpatient setting that is refractory to antiemetic treatment that embodies the challenge for patients living with HG and for clinicians caring for HG patients. Future RCTs, therefore, should focus on outcomes assessed in the outpatient setting in patients with refractory disease in order to truly assess the clinically meaningful benefit of an HG therapy.

Dr. Guttuso was the first to report on open-label gabapentin's benefit for refractory nausea and vomiting[15,16] and theorized that gabapentin may be effective for HG. An open-label pilot study was performed examining the tolerability and effectiveness of gabapentin in the treatment of HG (see Appendix).[17]

Preliminary studies:

This clinical study protocol was first submitted to the FDA as Investigational New Drug (IND) 79,612 and was approved by the University at Buffalo's Institutional Review Board (IRB), and later by the Sisters of Charity Hospital's IRB, before any subjects were enrolled. All subjects provided written informed consent.

We initially enrolled 7 subjects with HG from March 2008-March 2009. Subjects were supplied with gabapentin 300mg capsules and took the first dose at the time of enrollment. They were given instructions on how to slowly increase the dose to a minimum of 1,200mg/day and a maximum of 3,600mg/day. After 14 days of therapy, gabapentin was discontinued for 2 days to determine if symptoms recurred. If there was a > 50% increase in nausea or vomiting while off gabapentin, gabapentin could be resumed on Day 17 and for the remainder of the pregnancy, if necessary.

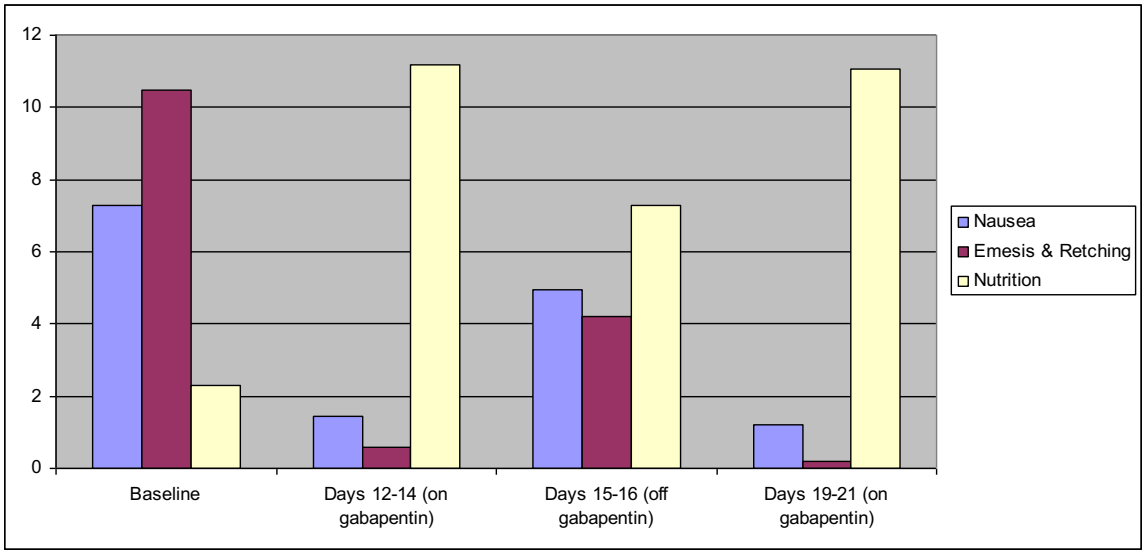
The primary outcome measures were percent reduction in nausea and emesis/retching from Baseline to the mean of Days 12-14 based on subjects' daily recordings on the validated Motherisk-PUQE (pregnancy-unique quantification of nausea and emesis) diary.[18]

Results:

The median gestational age at the time of enrollment was 8 weeks. All 7 subjects had at least 3+ ketonuria and >5% weight loss from their pre-pregnancy weight at Baseline. The mean number of anti-emetics tried before enrolling was 2.4. The first 3 subjects were enrolled as inpatients and managed as outpatients while the other 4 subjects were enrolled and managed as outpatients. Gabapentin's onset of action appeared to be very rapid with all 7 subjects experiencing a ≥50% decrease in nausea by Day 2 of gabapentin therapy and complete resolution of emesis by Day 4. The 3 subjects enrolled as inpatients were discharged 2, 3, and 2 days after starting gabapentin, respectively.

None of the subjects required admission/readmission for hyperemesis after starting gabapentin. The mean reductions in nausea and emesis from Baseline to Days 12-14 were 80% and 94%, respectively, and 84% and 98%, respectively, from Baseline to Days 19-21.[19] There was a >3x increase in mean nausea and a >7x increase in mean emesis scores associated with discontinuing gabapentin during Days 15-16. These data and oral nutrition scores are summarized in Figure 1. Subjects gained an average 0.85 pounds from Baseline to Day 21. The mean maximum daily gabapentin dose was 1,843mg.

Figure 1: Mean nausea, emesis and nutrition scores (*n*=7)




On Day 12, the amount of relief experienced from gabapentin on the 7-point Likert scale was reported as "6" by 4 subjects and "7" by 3 subjects. The degree of satisfaction with gabapentin was recorded as "Satisfied" by 4 subjects and "Very Satisfied" by 3 subjects.

Subjects 8 & 9 were enrolled as inpatients and had been reporting excellent benefit from the gabapentin therapy until Days 15-16 when they discontinued gabapentin and subsequently experienced severe recurrence of HG symptoms. These 2 subjects failed to complete any of their Motherisk-PUQE diaries.

Subject 10 was enrolled as an inpatient and experienced a 100% resolution of emesis and a near full resolution of nausea and impaired nutritional intake by Days 12-14. She discontinued gabapentin after 10 weeks of therapy and did well for 2 weeks but then had recurrence of refractory HG and was admitted to the hospital. After failing to respond to intravenous metoclopramide, ondansetron and prochlorperazine, she resumed gabapentin and experienced full resolution of symptoms.

Subject 11 was enrolled as an inpatient at 10 weeks gestation and experienced full resolution of nausea, emesis and anorexia after initiating gabapentin. This subject was able to discontinue gabapentin after 4 weeks without recurrence of symptoms.

Four subjects experienced mild-moderate side effects of sleepiness or dizziness when first starting gabapentin. These side effects did not interfere with any activities of daily living and dissipated or resolved by the second week of therapy in all 4 subjects.

Two of these 11 subjects from our pilot study were lost to follow/up despite multiple attempts at contact. Eight of the other 9 subjects delivered at term and one baby

was found to have hydronephrosis eventually requiring surgical correction. The other subject delivered twins by C-section at 33 weeks gestation. This pregnancy was conceived via in-vitro fertilization (IVF). One twin had a tethered spinal cord and a lumbar skin tag requiring surgical correction while the other twin had no congenital defects. These congenital defects have been reported to the FDA under IND 79,612.

In addition to the 11 subjects enrolled into the pilot study, another HG patient was treated with gabapentin by a local nurse practitioner (NP) who was familiar with our research. This patient had a history of HG with 3 previous pregnancies all of which were electively terminated due to severe and medically refractory nausea and vomiting. The patient again developed nausea and vomiting with the current pregnancy starting at 6 weeks gestation. She was started on metoclopramide 10mg qid x 3 weeks and, subsequently, ondansetron 4mg q4 hours was added for persistent nausea and vomiting. At 12 weeks gestation the patient had lost 10 pounds over the previous week (=4.3% of her pre-pregnancy weight), was found to have 3+ ketonuria, and was no longer able to work as a nurse due to persistent nausea and vomiting despite taking both metoclopramide and ondansetron, as prescribed. She told her NP that she was going to have to terminate the pregnancy due to the severe and medically refractory symptoms and her inability to work.

After the NP informed the patient on the promising results from the pilot study, the patient agreed to first try gabapentin before making a final decision to terminate the pregnancy. After receiving 3 liters of iv hydration, the patient started gabapentin 300mg tid on 7/19/11 at 12 weeks gestation. By the afternoon of 7/20/11, the patient reported that her nausea and vomiting had improved by about 90% and she was having no difficulty tolerating normal oral nutrition and hydration. Within a few days, the patient returned to her nursing job full-time and continued to work until she delivered. The patient also did not require any more iv hydration throughout the pregnancy. On 9/9/11, gabapentin was increased to 300mg bid and 600mg qhs for some recurrent symptoms with good response. The patient continued to take metoclopramide and ondansteron, as needed, which was 1-2x/week. Metoclopramide and ondansetron were discontinued at week 21 and 26 gestation, respectively. Gabapentin was continued until spontaneous labor began at 38 weeks gestation. A healthy baby was delivered by Caesarian section 2 days later.

Only 1 of the 12 patients treated with gabapentin for HG to date has required hospital admission/readmission for HG, which occurred 12 weeks after initiating gabapentin. This markedly contrasts the 20-40% readmission rate within 2 weeks of enrollment observed in previous HG trials.[1,8,11,14]

The promising results from our pilot study and from this additional case using gabapentin for HG have been consistent with our previous experiences using gabapentin in other patient populations experiencing severe and refractory nausea and/or emesis.[15,16] Subsequent to our initial reports on this novel use of gabapentin, several other groups have performed RCTs showing gabapentin to have significant benefit in the prevention or treatment of nausea and vomiting.[20-22]

Gabapentin's main clinical use is in the treatment of neuropathic pain, which is one of its FDA-approved indications. Gabapentin's mechanism of action in this condition is mediated through its specific neuronal binding site, the alpha-2/delta subunit of voltage-gated calcium channels (VGCCs),[23,24] most likely by acting as a calcium

channel antagonist.[25,26] In the leading animal model of neuropathic pain, alpha-2/delta subunits were shown to upregulate 17x in sensory neuronal cell bodies in response to an experimental nerve lesion associated with allodynia and neuropathic pain.[27] It has been theorized that this dramatic upregulation in alpha-2/delta subunits is not only involved in the pathophysiology of neuropathic pain but also is what offers the opportunity for gabapentin's clinical efficacy in this condition.[27] It has also been theorized that upregulation in this subunit in the nervous system's temperature regulatory centers in response to plummeting estrogen levels at menopause is involved with the pathophysiology of hot flashes and accounts for gabapentin's effectiveness in relieving hot flashes and night sweats.[28]

In the treatment of HG, we theorize that gabapentin mitigates calcium currents in nausea/vomiting centers (such as the area postrema of the medulla) by binding to alpha-2/delta subunits of that have been upregulated in response to the dramatic increases of estrogen and progesterone early in pregnancy.

In terms of gabapentin's safety during pregnancy, there have been 5 infant major congenital malformations (MCMs) reported among 294 first trimester gabapentin monotherapy exposures.[17,29-32] Two of these 5 MCMs were from our pilot study, as described above. This equals a 1.7% rate (5/294) of infant MCMs. Comparing this rate with that found in the general population, the rate of MCMs detected by the end of the first week of life in the Metropolitan Atlanta population between 1968 and 2003 was 2.1%,[33] while the Brigham and Women's Hospital Surveillance Program reported a MCM frequency of 1.6%–2.2% at birth depending on whether chromosomal and genetic abnormalities were included in the calculation.[34]

In conclusion, open-label gabapentin appears to be well tolerated and effective in the treatment of HG. It also does not appear that first trimester use of gabapentin is associated with any increased risk of infant MCMs compared to the general population. Due to the current lack of any effective HG therapy, a RCT using gabapentin for HG is merited. As noted above, the growing body of literature supporting a significant antiemetic effect of gabapentin in other patient populations[20-22] further supports the merits of continued research on its effects in HG.

We initiated a RCT in 7/2014 comparing the efficacy of gabapentin with ondansetron in women with HG and have enrolled 7 subjects as of 6/14/15. However, recently several eligible patients have informed us that they did not want to participate in this study due to the publicity stemming from 2 recent studies associating maternal use of ondansetron with increased rates of congenital cardiac septal defects.[35,36] The Andersen et al. study[35] has received much media attention, despite the fact that it has not yet been published in a peer-reviewed journal, due to the 12/2014 publication of an opinion article that highlighted this potential risk of ondansetron and recommended against its use in pregnancy.[37] Even though a previous report did not associate maternal ondansetron use with increased rates of congenital defects,[38] I suspect that once the Andersen et al. study is formally published, there will be more media attention on this issue, which will serve to make it even more difficult for us to enroll into our current clinical trial if we maintain the ondansetron treatment arm.

Due to this new information, that was not anticipated at the time that our study protocol was approved, we requested approval from the NIH to change the ondansetron treatment arm to a metoclopramide treatment arm. On 6/5/15, the NIH approved this

change.

To date, there have been 3 large studies all demonstrating metoclopramide use to be safe during pregnancy without any increased risk for congenital defects.[35,39,40] There have been no contradictory studies. Interestingly, the Andersen et al. study was one of these studies as this group used first trimester metoclopramide exposures as a control group.[37] This finding will further strengthen the evidence supporting the safety of metoclopramide use in pregnancy once the Andersen et al. study is formally published. We anticipate that this safety information will be very reassuring to potential study subjects and, as a result, will lead to greatly improved enrollment after changing the ondansetron arm to metoclopramide.

Although ondansetron is considered to be one of the most effective therapies for HG in common practice, this has not been confirmed in controlled trials when compared to metoclopramide. A recent randomized controlled trial showed ondansetron to have equivalent efficacy to metoclopramide among 160 subjects with HG.[41] An earlier randomized controlled trial showed ondansetron to only have a significant trend towards being more effective than metoclopramide for reducing vomiting but not nausea among 83 women with HG.[42]

We conclude that these safety and efficacy data support the use of metoclopramide over ondansetron as the most appropriate treatment arm to compare with gabapentin in our current trial.

Our trial has enrolled 7 subjects, to date. Most likely only 3 or 4 of these subjects have been randomized to ondansetron. Therefore, changing this treatment arm at this early stage should not appreciably affect data evaluation at study completion. We will combine the data from subjects receiving ondansetron, to date, and future subjects receiving metoclopramide for analyses of our primary and secondary study endpoints.

*2.4 Include complete specific citations/references.*

Response:

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## 3.0 Inclusion and Exclusion Criteria

*3.1 Describe the criteria that define who will be included or excluded in your final study sample.*

Response:

**<u>Eligibility Criteria</u>:**

1) Have received at least 2 administrations of intravenous (iv) hydration separated by at least 1 week **or** daily emesis for at least the last 7 days and 1 administration of iv hydration.
2) Have at least one of the following: 2-4+ ketonuria, serum potassium < 3.4mmol, or >5% weight loss from weight upon entry to prenatal care at any time during the current pregnancy.
3) Have failed therapy with at least one antiemetic.
4) Have fetal ultrasound within 6 weeks prior to enrollment confirming a normal-appearing, intrauterine, singleton pregnancy of gestational age < 16 weeks at time of enrollment.
5) Felt by the patient's obstetrician or emergency room attending physician not to have other medical problems such as bowel obstruction, pancreatitis, biliary colic, or peptic ulcer disease that could be contributing to the patient's symptoms.
6) Be >18 years old and not decided to terminate the pregnancy.
7) Have not received or planning to receive a peripherally inserted central catheter (PIC line).
8) Have a Motherisk-PUQE score of ≥12 for the 24-hour Baseline period.
9) Felt not to have any other significant medical, psychiatric or substance abuse problem that would preclude participation in the study.
10) Agrees to discontinue any current anti-emetic treatments (including antihistamines, ginger, > 10mg/day vitamin B6, serotonin or dopamine antagonists, anticholinergics, acupuncture, hypnosis, or wrist bands) for the next 3 weeks.

11) Pregnancy not conceived through in-vitro fertilization.

12) Has not previously tried gabapentin for hyperemesis

13) No previous evidence of intolerance to metoclopramide

14) Able to understand and comply with the study procedures and give informed consent.

15) Not currently enrolled in another research study.

*3.2 Describe how individuals will be screened for eligibility.*

Response:

Referred subjects will be interviewed to assess for eligibility. Eligible subjects will be given a verbal overview of the study and then provided with a copy of the Consent Form to review. After the subject has reviewed the Consent Form all questions will be answered and subject comprehension of study procedures will be confirmed before written consent is obtained.

*3.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of these populations as subjects in your research unless you indicate this in your inclusion criteria.)*

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

Response: This study will include pregnant women (at 18 years old) who have the capacity to provide consent. Adults who do not have the capacity to consent, and prisoners will not be included.

*3.4 Indicate whether you will include non-English speaking individuals. Provide justification if you will exclude non-English speaking individuals.*
*(In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may not be routinely excluded from research. In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English: e.g., pilot studies, small unfunded studies with validated instruments not available in other languages, numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.)*

Response: The validated questionnaires are not available in non-english translation.

## 4.0 Study-Wide Number of Subjects (Multisite/Multicenter Only)

*4.1 If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.*

Response: A total of 60 women with HG will be enrolled into this study.

## 5.0 Study-Wide Recruitment Methods (Multisite/Multicenter Only)

*If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described later in the protocol.*

*5.1 Describe when, where, and how potential subjects will be recruited.*

Response: Dr. Thornburg and Dr. Guttuso have provided information about the study to providers with contact information for the study team for the purpose of potential subject referrals.

*5.2 Describe the methods that will be used to identify potential subjects.*

Response: Providers will notify the study team of potential study subjects, based on meeting basic inclusion criteria. In addition, study personnel will use the electronic medical record to screen ER patients at the study's enrolling hospitals. ER patients who may be eligible for this study will only be approached or contacted after obtaining approval from their Ob/Gyn and ER provider. A HIPAA waiver for these activities is currently approved by the IRB.

*5.3 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)*

Response: Flyers for providers in the ED at WCHOB, Sisters of Charity Hospital, and Millard Fillmore Suburban Hospital. Patient flyer for display and distribution at private OB/GYN offices and ED waiting rooms.

## 6.0 Multi-Site Research (Multisite/Multicenter Only)

*6.1 If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:*

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*

- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.*

Response:

All sites have the most current version of the protocol, consent document, and HIPAA authorization.

All required approvals have been obtained at each site (including approval by the site's IRB of record).

All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.

All engaged participating sites will safeguard data as required by local information security policies.

All local site investigators conduct the study appropriately.

All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.

*6.2 Describe the method for communicating to engaged participating sites:*

- *Problems.*
- *Interim results.*
- *The closure of a study*

Response:

Any problems, new information regarding the study medications, changes in study status, or reports of AE or SAE's will be reported to the safety monitor, and IRB as per local policy, and also to the other participating sites in a timely manner.

## 7.0 Study Timelines

*7.1 Describe the duration of an individual subject's participation in the study.*

About 3-24 weeks depending on the symptomatic need for therapy and the subject's delivery date.

*7.2 Describe the duration anticipated to enroll all study subjects.*

Response: 12/31/2017

*7.3 Describe the estimated date for the investigators to complete this study (complete primary analyses)*

Response: 12/31/2017

# 8.0 Study Endpoints

*8.1 Describe the primary and secondary study endpoints.*

Response:

**Study Endpoint:**

The Study Endpoint will be the mean values from Days 5-7.

**Primary Outcome Measure:**

Mean percent change from Baseline to the Study Endpoint in daily Motherisk-PUQE scores (pregnancy-unique quantification of emesis and nausea scale).

**Secondary Outcome Measures:**

i) Mean percent change from Baseline to the Study Endpoint in daily nausea and emesis/retching scores individually from the Motherisk-PUQE and from the raw data.

ii) Mean percent change from Baseline to the Study Endpoint in daily oral nutrition scores.

iii) For subjects enrolled as inpatients, number of days from enrollment to hospital discharge.

iv) Percent of subjects requiring repeat iv hydration or hospital admission for HG from the outpatient setting.

v) Mean percent change in NVPQOL[39] questionnaire scores from Baseline to the Study Endpoint.

vi) Mean satisfaction and mean relief scores at the Study Endpoint as determined by the Satisfaction Questionnaire.

vii) Percent of subjects downgrading from an answer of 3-5 at Baseline to 1-2 at the Study Endpoint on the Hyperemesis Gravidarum Pregnancy Termination Consideration (HGPTC) questionnaire.

viii) Percent of subjects choosing to continue their experimental therapy at the Study Endpoint as determined by question 3 on the Satisfaction Questionnaire.

ix) Maternal side effects and pregnancy outcomes (maternal complications, term of delivery, mode of delivery, congenital malformations, newborn complications).

x) Mean percent change in laboratory values and weight from Baseline to Day 8.

xi) Mean percent change from Baseline to Days 20-22 in daily Motherisk-PUQE and NVPQOL scores (during open-label gabapentin treatment).

xii) Mean Satisfaction Questionnaire scores at Day 22.

xiii) Percent of subjects downgrading from an answer of 3-5 at Baseline to 1-2 at Day 22 on the HGPTC questionnaire.

*8.2 Describe any primary or secondary safety endpoints.*

Response: N/A

## 9.0 Procedures Involved

*9.1 Describe and explain the study design.*

Response: Randomized, double-blinded, 2-arm, parallel-design comparative clinical trial (gabapentin vs. metoclopramide).

*9.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.*

Response: If eligibility is confirmed, a venous blood draw will be performed to be tested for screening blood work consisting of a complete blood count with platelets, a chemistry profile including liver function tests (AST, ALT, and total bilirubin), and a thyroid stimulating hormone (TSH) level. A fetal ultrasound will only be performed if one hasn't been performed within the previous 6 weeks.

Subjects will receive instructions (verbal and written) on how to complete the Patient Data Form, which they will complete every day for the **next 21 days.** Gabapentin 300mg or metoclopramide 7.5mg will be identically-appearing and will be initiated as follows: 1 capsule at the time of enrollment and 1 capsule at bedtime on Day 1; 1 capsule in the morning, 1 capsule in the afternoon, and 1 capsule at bedtime on Day 2; 1 capsule in the morning, 1 capsule in the afternoon, and 2 capsules at bedtime on Day 3; 1 capsule in the morning, 2 capsules in the afternoon, and 2 capsules at bedtime on Day 4; and then 2 capsules tid on Days 5-7. For subjects still experiencing bothersome nausea or vomiting after Day 5, the dose can be increased to 2 capsules qid for Days 6-7. Gabapentin serum ½ life in humans is 5-7 hours, therefore, tid or qid dosing provides adequate full day coverage. A maximum of 8 capsules a day equates to 2,400mg of gabapentin or 60mg of metoclopramide a day. The gabapentin dose titration has been chosen based on our experiences with efficacy and

tolerability of gabapentin over the initial 14 days of treatment in our pilot study. Out of the 12 HG patients receiving gabapentin, 11 experienced satisfactory relief at a maximum dose of 2,100mg/day or less, while 1 subject required 2,700mg/day. The maximum FDA-approved oral metoclopramide dose is 60mg a day for treating nausea and vomiting recommended maximum oral metoclopramide dose is 60mg a day for treating nausea and vomiting..[41]

The titration schedule can be slowed and/or the total daily dose decreased if bothersome side effects occur or if the subject requests due to adequate symptom control. Subjects will be contacted by phone at least 4 times a week by voice call or text for the first 7 days to monitor subjects' HG symptoms, to monitor for any study drug-related side effects, to confirm that subjects are filling out the Patient Data Form every day and to answer questions. If a subject cannot be reached at the primary phone number, all secondary numbers will be called. If a subject cannot be reached after 3 days, a letter will be sent to their address instructing them to call the study team immediately. Each subject will be supplied with a bottle of urine ketone strips. More symptomatic subjects with daily vomiting will be instructed to check their urine ketones every day and to contact the study team for readings of 2-4+ ketones. More symptomatic subjects will be contacted by phone by the study team every day to confirm that urine ketones are being checked and to monitor for other symptoms of dehydration, such as lightheadedness or dizziness. Subjects with 2-4+ urine ketones who are experiencing frequent vomiting or poor oral hydration and subjects otherwise felt to have symptomatic dehydration will be told to see their obstetrician or go to the ER that day for further evaluation. All subjects' obstetricians will be notified of their participation in this study.

**On about Day 8,** subjects will return for a **follow-up visit (Visit 2)** and will bring their completed Data Forms, and all unused study drug with them. If the subject is admitted to the hospital on Day 8, this visit will occur at their bedside. At this visit, the Patient Data Forms will be collected and, for subjects who had not received repeat iv hydration during the study, the NVPQOL, HGPTC and Satisfaction questionnaires will be completed. A venous blood draw will be performed and tested for the screening blood work. Subjects will be asked about adverse events, concomitant medications/treatments, and weight and urine ketone level will be recorded.

Subjects who have not withdrawn from the study will be offered open-label gabapentin treatment at Visit 2 that can be continued for the remainder of the pregnancy, if necessary. The open-label gabapentin titration will be repeated as described above. Subjects will be informed that they may have recurrent symptoms during this titration period. In addition, metoclopramide 10mg po qid prn breakthrough vomiting can be used during the open-label phase. Subjects will be instructed to limit the

use of metoclopramide for breakthrough nausea or vomiting to 4 times a day, not to exceed 40mg. The Open Label Patient Data Form will be filled out daily for an additional 14 days and brought, along with any unused study drug to the **final follow-up visit (Visit 3) on about Day 22**. If the subject is admitted to the hospital on Day 22, this visit will occur at their bedside. At this visit, the Patient Data Forms will be collected and the NVPQOL, HGPTC and Satisfaction questionnaires will be completed. A venous blood draw will be performed and tested for the screening blood work. Subjects will be asked about adverse events and concomitant medications/treatments, and weight and urine ketone level will be recorded. Subjects in the open label phase of the study will be followed up with weekly to assess any adverse events or side effects. Subjects will be instructed to call the study team sooner if necessary. Subjects will be supplied with enough gabapentin and prn metaclopromide to last until 18 weeks gestation. However, if a subject has been taking metoclopramide for 12 weeks, it will be discontinued to minimize the risk of tardive dyskinesia (<1%). Subjects needing additional relief from breakthrough nausea and vomiting will be instructed to discuss the options with their OB/GYN provider. Only the lowest effective gabapentin dose will be used. Based on the site investigator's discretion, subjects may be supplied with additional gabapentin at 4 weeks intervals after 18 weeks gestation.

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

Response: After enrollment, subjects will be followed up with daily or every other day depending on symptom severity, and will be asked about side effects, and oral intake status. Subjects will be provided with ketone strips and recommendations for IV fluids will be made as necessary. The PI and study coordinator are available for contact at any time, should the subject have questions or experience side effects. Titration to the ideal dose will occur at the start of the study and appropriate dose adjustments can be made at the discretion of the PI if bothersome side effects occur.

Subjects will be informed, in writing, about the current state of knowledge regarding gabapentin's safety in pregnancy during the informed consent process. Subjects will also be updated with any new safety information regarding gabapentin use during pregnancy or distinct from pregnancy that comes to light after they are enrolled. Drs. Guttuso and Thornburg will review and sign/date weekly all case report forms, data forms and adverse event forms at each respective site.

*9.3 Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.*

Response: Gabapentin is currently approved by the Food & Drug Administration (FDA) for the treatment of certain types of pain, seizures, and restless legs syndrome (the urge to keep moving the legs while laying or resting). Gabapentin is being used in this study for the treatment of

hyperemesis gradivdarum related nausea and vomiting. The Food & Drug Administration (FDA) has reviewed all current safety and efficacy data regarding the use of gabapentin during pregnancy and for HG and has issued the active IND 079,612.

Maternal use of metoclopramide (Reglan), has not been associated with any increased rate of congenital defects in over 30,000 exposures (see Background and Significance section).

*9.4 Describe the source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)*

Response: data will be collected through the use of:

Patient Data forms (daily diary)

Hyperemesis Gravidarum Pregnancy Termination Consideration Questionnaire (HGPTC)

The Nausea and Vomiting of Pregnancy Quality of Life Questionnaire (NVPQOL)

Satisfaction Questionnaire

(All above documents are currently approved by UBIRB)

*9.5 What data will be collected including long-term follow-up.*

Response: data regarding symptom severity/frequency, oral intake, satisfaction of symptom resolution, consideration of pregnancy termination and quality of life measures will be collected in the blinded and open label phases. Subjects will be followed until delivery and hospital records as well as babies' pediatrician records will be assessed for maternal and fetal outcomes.

*9.6 For HUD uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.*

Response: N/A. No HUD's being utilized in this study.

## 10.0 Data and Specimen Banking

*10.1 If data or specimens will be banked for future use, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

Response: N/A. No data or specimen banking will occur

*10.2 List the data to be stored or associated with each specimen.*

Response: N/A. No data or specimen banking will occur

*10.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.*

Response: N/A. No data or specimen banking will occur

## 11.0 Data Management

*11.1 Describe the data analysis plan, including any statistical procedures.*

Response:

The Biostatistics Department at the U of R, under the direction of Xin Tu, PhD, will update the data set at least weekly. Completeness of the data will be monitored by each site-PI at each subject visit when data forms will be reviewed. There will not be any interim analyses of the data.

All statistical tests are two-sided with $p<0.05$. Descriptive statistics (counts and proportions for categorical variables and means and standard deviations for continuous outcomes) will be used to depict the characteristics of the sample (e.g., age, race, insurance, number of prior pregnancy and relevant co-morbid conditions). We will also compare baseline characteristics across the two treatment conditions using methods appropriate to the data type such as t-tests, chi-square and/or Fisher's exact tests. We will also examine associations between the outcome variables and patients' characteristics. For those significantly associated with outcomes, we will treat them as covariates when constructing treatment comparisons (see below).

The primary as well as most of the secondary outcomes are change scores of pertinent variables over the two-week treatment period. We will model the change of such outcomes using longitudinal data methods based on the repeated assessments (e.g., pre-post changes and daily PUQE). For the outcomes that are collected once such as Satisfaction Questionnaire scores at Day 28, cross-sectional models such as t-test and regression (adjusting for the covariates identified) will be used to compare treatment differences.

We will use the two popular approaches, the weighted generalized estimating equations (WGEE) and the mixed-effects model (MM)[42-44], for modeling treatment differences over time. Both approaches will be used for assessing treatment differences, which provide valid inference in the presence of missing data if the missing value follows the missing at random (MAR) assumption, a popular mechanism that applies to most studies in practice.[43,44] If estimates differ between the two approaches, only WGEE results will be reported, as it provides significantly more robust inference, especially in the presence of missing data.[43-45] Given the relatively small sample size in the study, traditional inference based on the large sample theory may not provide accurate estimates. We may

complement the analysis with results based on clustered bootstrap methods.[46] We will perform intention-to-treat analyses using all subjects randomized to the treatment groups who have taken at least one dose of study medication and have provided at least 1 day of Patient Diary Data over the first week of the study. All analyses will be conducted using SAS 9.2 or later.

*11.2 Provide a power analysis.*

Response:

In our proposed RCT, we anticipate a more conservative treatment effect of at least 20% for the Primary Outcome Measure and a mean Baseline Motherisk-PUQE score of 22. Specifically, we anticipate a mean 70% decrease in Motherisk-PUQE scores for the gabapentin group (a decrease of 15.4 points, from 22 to 6.6) and a 50% decrease in Motherisk-PUQE scores for the ondansetron group (a decrease of 11 points, from 22 to 11). Therefore, we anticipate a 4.4 point difference (15.4-11) for the Primary Outcome Measure and we will assume a conservative SD of 6.

With these considerations, 30 subjects/group will provide 80% power to detect an inter-group difference in the Primary Outcome Measure with a two-sided type I error = 0.05. *Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.*

Response: Original subject data forms will be retained in each subject's individual study file and kept secured in a locked cabinet at each respective site. Data from the original forms will be entered onto a secure electronic database set up through the University of Rochester. Only study personnel will have access to entering data on this database. After study completion, Dr. Guttuso will bring the data forms from U of R to his locked office at UB. All data forms will have no subject identifiable information on them. There is no plan to release subject identifiers.

*11.3 Describe any procedures that will be used for quality control of collected data.*

Response: Drs. Guttuso and Thornburg will review and sign/date weekly all case report forms, data forms and adverse event forms at each respective site.

*11.4 Describe how data and specimens will be handled study-wide:*

Response: Data will be entered into a secured study database, by both sites study personnel, controlled by the University of Rochester. Only study team members have access to this site.

*11.5 What information will be included in that data or associated with the specimens?*

Response: questionnaire responses, diary data, adverse event data, IV hydration data, and study termination, and pregnancy termination data will be stored in the database. All data will be de-identified

*11.6 Where and how data or specimens will be stored?*

Response: original copies of the data will be stored in a study binder designated for each subject. Electronic data will be stored on the study database.

*11.7 How long the data or specimens will be stored?*

Response: Data will be stored for at least 3 years in accordance with US DHHS E6 GCP guidelines

*11.8 Who will have access to the data or specimens?*

Response: only IRB-approved study members will have access to the data. Data management personnel will have access to the database for maintenance or troubleshooting issues, however all data is de-identified.

*11.9 Who is responsible for receipt or transmission of the data or specimens?*

Response: Approved study personnel will transmit de-identified data onto the electronic data entry system

*11.10How data and specimens will be transported?*

Response: Data will be kept by the study coordinator from place of enrollment to a locked cabinet in the UB OB/GYN offices

## 12.0 Provisions to Monitor the Data and Ensure the Safety of Subjects

*12.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.*

Response:

The Data Monitoring Committee (DMC) will review the study's progress every 6 months and may perform an interim analysis of the data if so requested by the NIH. If there is a significant intergroup difference with a $p<0.001$ or an insignificant intergroup difference with a $p>0.70$, the DMC will be asked to consider terminating the study due to efficacy or futility rationale, respectively. The DMC will consist of: Eva K. Pressman, MD, Professor and Chair of Obstetrics & Gynecology, Director of Division of Maternal-Fetal Medicine, University of Rochester; J. Christopher Glantz, MD, MPH, Professor of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Rochester; Changyong Feng, PhD, Associate Professor of Biostatistics and Computational Biology, University of Rochester; and Sireesha Y. Reddy, MD, Professor and Vice Chair of Obstetrics & Gynecology, Texas Tech University Health Sciences Center in El Paso.**Adverse Events Review:**

**For <u>non-serious</u> subject adverse events:**

Subjects will be directly asked by one of the study team members about any adverse events during every contact, including the 3 scheduled study site visits. All adverse events (AE's) will be recorded on the AE report form and communicated within 7 business days to our Data Management Center at the University of Rochester. All AE's will be summarized in an Excel file and emailed monthly to the study's Safety Monitor, Patrick M. Mullin, MD, MPH, Assistant Professor of Obstetrics & Gynecology, University of Southern California.

**For <u>serious</u> subject adverse events:**

An adverse event will be considered "serious" (SAE) if in the opinion of either site Investigator (Drs. Guttuso and Thornburg) the adverse event resulted in subject death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. This is the definition of SAE according to the FDA's Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies.

When a study team member becomes aware of a possible subject SAE, the study team member will contact the site PI by phone the same day. The site PI will report the SAE to the study sponsor, Dr. Guttuso, by the following day.

An SAE that is determined by Dr. Guttuso to be a) unexpected, and b) reasonably possible to have been caused by either study drug will be considered a "Reportable Event". Dr. Guttuso will report such events to both of the study IRB's within 5 business days of the study team's first awareness of the event. Dr. Guttuso will also report the event to the FDA as an "IND safety report" within 7 calendar days of the study team's first awareness of the event, per the FDA's Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies. All SAE's will also be communicated to the Data Management Center and emailed to the Safety Monitor within 5 business days of the study team's first awareness of the event.

For example, if a subject was admitted to the hospital for symptoms of hyperemesis gravidarum, this would be considered an SAE; however, this would not be considered a "Reportable Event" since it was both anticipated in this patient population and not considered reasonably possible to have been caused by either study drug. On the other hand, an incident of Stevens-Johnson Syndrome or an infant congenital defect would be considered "Reportable Events" since they were serious, unanticipated and could possibly have been caused by either study drug.

<u>Flow Chart</u>:

**Day 1:** Study team member becomes aware of an SAE and alerts the site-PI.

**Day 2:** Dr. Guttuso is contacted by either the initial study team member who became aware of the SAE or by Dr. Thornburg, the study's other site PI.

**Day 3-5:** Any SAE determined by Dr. Guttuso to be a Reportable Event will be reported to both IRBs, the Safety Monitor and the Data Management Center.

**Day 3-15:** Dr. Guttuso will report the Reportable Event to the FDA as an IND Safety Report.

**Contact Information:**

Dr. Guttuso: 716-361-7957
Dr. Thornburg: 585-978-1925

*12.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.*

Response: See response to 12.1

*12.3 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).*

Response: information regarding adverse events will be obtained through text or voice calls with subjects, and then entered onto a hard copy form kept in the chart as well as in the electronic database.

*12.4 Describe the frequency of data collection, including when safety data collection starts.*

Response: data collection and safety data collection occurs upon enrollment.

*12.5 Describe who will review the data.*

Response: Maternal and fetal outcomes and adverse events will be reviewed monthly by the independent safety monitor, Patrick M. Mullin, MD, MPH, Assistant Professor of Obstetrics & Gynecology, University of Southern California... The PI will also review data weekly.

*12.6 Describe the frequency or periodicity of review of cumulative data.*

Response: Completeness of the data will be monitored by each site-PI at each subject visit when data forms will be reviewed.

*12.7 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.*

Response: N/A

*12.8 Describe any conditions that trigger an immediate suspension of the research.*

Response:

Dr. Guttuso will keep a log of Reportable Events. Subject enrollment will be halted and the Safety Monitor notified within 7 business days if any of the below thresholds are met:

| Number of Reportable Events | Total Number of Enrolled Subjects |
|---|---|
| 2 | 6 |
| 3 | 12 |
| 4 | 16 |
| 5 | 20 |
| 20% | All enrolled subjects |

The Safety Monitor will be asked to review all AE's and SAE's, including the reportable events, and make a recommendation on if the study protocol should be amended for subject safety or if the study should be terminated.

If the Safety Monitor recommends a protocol amendment, no further subjects will be enrolled until the amendment is approved by both IRB's and the FDA. Actively enrolled subjects will continue taking their study medications. If the Safety Monitor recommends study termination, all enrolled subjects will be contacted within 3 business days and informed that they should stop taking all study medications as the risks will then outweigh the potential maternal benefit. The NIH, both IRB's and the FDA will also be notified within 3 business days of the decision to terminate the study.

## 13.0 Withdrawal of Subjects

*13.1 Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.*

Response: A subject may be removed from the research study by the investigator if, it is believed that gabapentin is causing or contributing to potentially dangerous side effects.

*13.2 Describe any procedures for orderly termination.*

Response: If a subject is to be removed from the research study, the principal investigator will inform the subject of the decision to remove them from the research study and recommend appropriate follow up care thereafter.

*13.3 Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*

Response: Subjects' data will be collected until the point of study withdrawal. Subjects will be assessed for adverse events at the time of

withdrawal. Maternal and neonatal outcomes will still be collected after delivery following withdrawal from the study.

## 14.0 Risks to Subjects

*14.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.*

Response: Gabapentin is currently approved by the Food & Drug Administration (FDA) for the treatment of certain types of pain, seizures, and Restless Legs Syndrome. Gabapentin's most common side effects are sleepiness, dizziness, clumsiness, fatigue, and edema. About 7% of patients placed on gabapentin discontinue treatment due to side effects. Gabapentin has been in use since 1993 and has no known long-term side effects to the patient; i.e., when treatment is discontinued, the patient's side effects all resolve. In our pilot study using gabapentin for HG in 11 subjects, 57% of the subjects had mild-moderate sleepiness or dizziness that did not interfere with any activities of daily living and resolved or improved within a week. No other adverse events were felt to be related to gabapentin therapy.

The use of anti-seizure medications, in general, has been associated with a 0.21% increased risk of suicidal thoughts and behaviors (from 0.22% to 0.43%). It is not known if this increased risk applies to the use of gabapentin, in particular. Suicidal thoughts or behavior were not spontaneously reported by any of the 11 HG subjects receiving open-label gabapentin in our pilot study.

Gabapentin therapy has also been studied in pregnant rats and mice at many different doses to determine the risk for birth defects in the rodents' pups (Neurontin Package Insert). The FDA lists gabapentin as Pregnancy Category C. Two categories of congenital defects were observed in these preclinical studies: skeletal and renal. Delayed ossification of several bones were noted in the pups of pregnant mice and rats who received oral doses of gabapentin 1/2-4 times the maximum human dose of 3,600mg/day. The no effect dose for delayed ossification in mice was equivalent to a human dose of 1,800mg/day on a mg/m2 basis. Hydronephrosis and hydroureter were observed in the offspring of pregnant rats exposed to gabapentin. The no effect dose for hydronephrosis and hydroureter was equivalent to a human dose of 3,600mg/day. There were no other congenital malformations observed in the offspring of mice, rats, or rabbits given 4-8 times the maximum human daily dose on a mg/m2 basis.

In terms of gabapentin's safety during pregnancy in humans, there are 4 antiepileptic pregnancy registries that have reported on rates of infant

major congenital defects (MCMs) after first trimester gabapentin monotherapy exposure. With updated data now available from 2 pregnancy registries,[30,47] the total number of first trimester gabapentin monotherapy exposures with fetal outcome data is 258 (Table 1). Gabapentin was likely taken for the duration of most of these pregnancies as 75-100% of the mothers in these registries were being treated for epilepsy. The results from these 4 registries, from the gabapentin/HG pilot study and from 2 additional pregnancy cases treated with gabapentin are summarized in Table 1.

*Table 1: Summary of infant MCMs associated with 1rst trimester maternal use of gabapentin monotherapy*

| *Data Source* | *Total Exposures* | *MCMs* |
|---|---|---|
| *Montouris, et al.[31]* | *11* | *0* |
| *Morrow et al.[32]* | *31* | *1* |
| *Molgaard-Nielsen, et al.[30]* | *59* | *1* |
| *Hernandez-Diaz, et al.[47]* | *145* | *1* |
| *Guttuso, Jr., et al.[17]* | *10* | *2* |
| *Fujii et al.[48]* | *36* | *0* |
| *Additional Cases* | *2* | *0* |
| ***Summary*** | ***294*** | ***5(1.7%)*** |

Montouris, et al.[31]: No MCMs in infants of 11 patients on gabapentin monotherapy throughout their pregnancies.

Morrow et al.[32]: One MCM (ventricular septal defect) among 31 monotherapy exposures. All registered women had epilepsy.

Molgaard-Nielsen, et al.[30]: One MCM (congenital heart disease) among 59 monotherapy exposures. 75% of cohort had epilepsy.

Hernandez-Diaz, et al.[47]: One MCM (endocardial fibroelastosis with extensive hemagiomatosis) among 145 monotherapy exposures. 92% of cohort had epilepsy.

Guttuso, Jr., et al.[17]: Two MCMs (tethered spinal cord and hydronephrosis, both requiring surgical intervention) among 10 infants exposed to gabapentin monotherapy for HG. One MCM was from a twin pregnancy conceived through in-vitro fertilization, a technique associated with higher rates of infant MCMs.[49] These data were submitted to the FDA on 12/17/10.

Fujii et al.[48]: No MCMs among 36 infants exposed to first trimester gabapentin monotherapy. 34% of cohort used gabapentin for epilepsy.

No MCMs in 2 anecdotal first trimester gabapentin monotherapy exposures. One took gabapentin from preconception to gestation week 34 for epilepsy and the other from gestation weeks 12-38 for HG.

Thus, based on these initial 294 exposures, there has been a 1.7% rate of infant MCMs associated with maternal first trimester use of gabapentin monotherapy. Comparing this rate with that found in the general population, the rate of MCMs detected by the end of the first week of life in the Metropolitan Atlanta population between 1968 and 2003 was 2.1%,[33] while the Brigham and Women's Hospital Surveillance Program reported a MCM frequency of 1.6%–2.2% at birth depending on whether chromosomal and genetic abnormalities were included in the calculation.[34]

Although it has been estimated that about 555 exposures are needed to detect a 2-fold increase in MCM rate with 80% power,[50] it is reassuring that there does not appear to be a trend towards increased risks compared to the general population among the initial 258 gabapentin monotherapy exposures.

When considering other newer-generation antiepileptic drugs used during the first trimester, the rates of MCMs have remained fairly stable from an initial 182 or more exposures to 495 or more exposures. For example, an initial 182, 197 and 197 exposures to oxcarbazepine, levetiracetam and topiramate showed MCM rates of 2.2%, 2.0% and 4.1%, respectively.[47,50] After a total of 575, 530 and 495 exposures to oxcarbazepine, levetiracetam and topiramate the MCM rates were then 2.6%, 2.1% and 4.4%, respectively.[30,32,47] Thus, there was a 5-18% increase in MCM rates observed with additional exposures for these 3 newer-generation antiepileptic drugs. Based on these historical data, one would expect similar findings after additional exposures to the newer-generation antiepileptic drug gabapentin. Even if there was a maximum 18% increase in the MCM rate after an additional 300 gabapentin exposures, that would equate to an MCM rate of about 2.0%, which is still approximately equivalent to the MCM rate found in the general population.[33]

The FDA cited particular concern regarding the single case of hydronephrosis in one of the infants from the gabapentin/HG pilot study due to the increased rates of hydronephrosis found in the preclinical studies referenced above. Primarily due to this single case of hydronephrosis, the FDA placed a Full Clinical Hold on our

Investigational New Drug (IND) application #079612 on 4/8/11. The above data were submitted to the FDA on 4/23/12 in support of this IND. On 5/24/12, Dr. Guttuso received a "Remove Full Clinical Hold" letter from the FDA stating, "We have completed the review of your submission, and have concluded that the clinical trial can be resumed". The last IND annual report was submitted to the FDA on 8/2/15 and this IND remains open and active.

It is reassuring that there have been no other cases of hydronephrosis reported among the other 257 infants exposed to gabapentin in the first trimester, which equates to a hydronephrosis rate of 0.4%. The prevalence of hydronephrosis in the general population of newborns has been shown to be about 0.5%;[51] however, a more recent study showed a 2% rate of ultrasound-diagnosed, antenatal urologic findings, such as hydronephrosis, among 1000 consecutive births.[52] These studies, however, did not report on the rates of severe hydronephrosis necessitating surgical intervention, such as the case from the gabapentin pilot study. Nevertheless, it is reassuring that first trimester gabapentin exposure currently does not appear to be associated with higher rates of infant hydronephrosis in humans.

Alternative treatments for HG, which will be disclosed in the informed consent, include ginger, vitamin B6, compazine, metoclopramide, methylprednisolone, and ondansetron.

The use of metoclopramide during the first trimester of pregnancy has not been associated with any increased risk for physical birth defects among over 30,000 infants. It is not known if taking gabapentin or metoclopramide during pregnancy will affect development after birth but no such risks have been identified to date.

The most common side effects caused by metoclopramide are sleepiness, diarrhea and restlessness. Metoclopramide can rarely (<1%) cause movement problems such as hand shaking, slowed walking, muscle stiffness or abnormal movements in the face or neck (tardive dyskinesia). With prolonged use of metoclopramide (>12 weeks), some of these movement problems can be permanent even after stopping metoclopramide. For this reason, if a subject chooses to enroll in this study, we will ask them to stop taking metoclopramide if they are still taking it 12 weeks after enrolling into this study.

*14.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.*

Response: there are no procedures associated with this study.

*14.3 If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.*

Response: See response to 14.1

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

Response: N/A

## 15.0 Potential Benefits to Subjects

*15.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.*

Response: Subjects may experience a reduction in their HG symptoms. If gabapentin is found to be an effective treatment for HG in this RCT, it could markedly improve the quality of life for patients with HG, decrease the over 50,000 hospital admissions in the US every year for HG, increase work hours for women with HG, and potentially decrease the approximate 9,000 pregnancies terminated each year in the US due to HG (15% of 60,000 annual HG patients).

*15.2 Indicate if there is no direct benefit. Do not include benefits to society or others.*

Response: N/A

## 16.0 Vulnerable Populations

*16.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.*

- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information.*
- *If the research involves neonates of uncertain viability or non-viable neonates, review "CHECKLIST: Neonates (HRP-413)" or "HRP-414 – CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provided sufficient information.*
- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information.*

- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information.*
- *Consider if other specifically targeted populations such as students, employees of a specific firm or educationally/economically disadvantaged persons are vulnerable to coercion or undue influence. The checklists listed above for other populations should be used as a guide to ensure that you have provided sufficient information.*

Response: The consent document will be reviewed in full detail with potential subjects. Details regarding the currently available information on gabapentin exposure in pregnant women and its potential effects to the fetus will be explained in-depth and comprehension by the enrollee will be confirmed.

## 17.0 Community-Based Participatory Research

*17.1 Describe involvement of the community in the design and conduct of the research.*

Response: N/A

*Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.*

## 18.0 Sharing of Results with Subjects

*18.1 Describe whether or not results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.*

Response: study results will be shared with subjects after the completion of the data analysis for the study. Any new findings related to a subject's condition or care throughout the duration of the study will be communicated to the subject and if applicable, their primary care provider or OBGYN. Any new information about the investigational medication during the study will be communicated to subjects promptly.

## 19.0 Setting

*19.1 Describe the sites or locations where your research team will conduct the research.*

Response: Subjects are being enrolled from Women & Children's Hospital of Buffalo, Sisters of Charity Hospital, Millard Fillmore Suburban Hospital, and Dent Neurological Infusion Center. Referrals to this study can be made from VNA of WNY and MacAuley-Seton.

*19.2 Identify where your research team will identify and recruit potential subjects.*

Response: Subjects are being enrolled from the emergency departments or inpatient units at Women & Children's Hospital of Buffalo, Sisters of Charity Hospital, Millard Fillmore Suburban Hospital, or as outpatients by referrals from VNA of WNY and MacAuley-Seton home infusion services, and the Dent Neurologic Infusion Center.

*19.3 Identify where research procedures will be performed.*

Response: Initial procedures (consenting and baseline questionnaires) will be performed either in the ED, inpatient setting, or the womens health clinic at WCHOB. Follow-up visits will occur at WCHOB's Women's Health Clinic

*19.4 Describe the composition and involvement of any community advisory board.*

Response: N/A

*19.5 For research conducted outside of the organization and its affiliates describe:*

- *Site-specific regulations or customs affecting the research for research outside the organization.*
- *Local scientific and ethical review structure outside the organization.*

Response: The IRB for the Catholic Health system, as well as the IRB for the University of Rochester also review this study as needed.

## 20.0 Resources Available

*20.1 Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform their role. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research. Note- If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that person meets the qualifications described to fulfill their roles.*

Response:

**Thomas Guttuso, Jr., MD- Principal Investigator**; Associate Professor of Neurology, Obstetrics & Gynecology; extensive prior experience conducting clinical trials.

**Rachel LaPorta, MA, BSN, RN** – Primary Study coordinator; Previous experience working as an IRB administrator and as a clinical research coordinator for various industry sponsored and investigator initiated clinical trials. Currently working on various projects as a clinical research coordinator for the UB OB/GYN department.

*Describe other resources available to conduct the research: For example, as appropriate:*

*20.2 Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*

Response: There will be 2 enrolling sites: University at Buffalo, Buffalo, NY (UB) and University of Rochester, Rochester, NY (U of R). The PI, Dr. Guttuso at UB, and the Co-investigator, Dr. Thornburg at U of R, will perform or direct all of the study activities. We anticipate enrolling about 24-30 subjects/year, in total, based on recent HG presentation rates.

*20.3 Describe the time that you will devote to conducting and completing the research.*

Response: PI: 33% ; Study Coordinator 33%

*20.4 Describe your facilities.*

Response: All study visits will occur in a hospital or clinic setting depending on patient status (ED, inpatient or outpatient). All settings have private areas where study visits can be conducted in confidence.

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

Response: The principal investigator and co-investigator are both medically trained physicians to provide medical care or referral to the appropriate provider in the event of consequences requiring reporting/follow-up associated with this research. Any adverse events will be documented and communicated to other providers involved in the subject's care.

*20.6 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.*

Response: All study personnel duties are outlined on the core data form. Prior to addition of study staff and approval by the IRB, roles are reviewed and agreed upon based on clinical skill. All required protocol training and

GCP training is documented. Experience and expertise of study staff is taken into consideration and study staff roles are in compliance with the protocol.

## 21.0 Prior Approvals

*21.1 Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)*

Response: IRB Approval obtained.

## 22.0 Recruitment Methods

*22.1 Describe when, where, and how potential subjects will be recruited.*

Response: After notification by a provider to a study team member, subjects will be recruited upon presentation to the ED or inpatient unit and will be consented there.

*22.2 Describe the source of subjects.*

Response: Subjects will be referred by providers in the inpatient setting, ED or outpatient clinic setting from WCHOB, MFS or SOCH. WNY VNA and McAuley-Seton Home Care, and Dent Neurologic Infusion Center, will also refer interested home-infusion patients diagnosed with hyperemesis gravidarum.

*22.3 Describe the methods that will be used to identify potential subjects.*

Response: Providers are given a basic list of criteria that could qualify a subject for the study. If a subject qualifies based on the basic criteria, a member of the study team is contacted to interview the patient further and obtain consent.

*22.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)*

Response: recruitment methods include verbal description of the study (prior to presenting consent form); post cards mailed to private practices (for providers); patient flyers to be posted in private practice offices

*22.5 Describe the amount and timing of any payments to subjects.*

Response: Subjects will be reimbursed for parking for follow-up visits at the Women's Health Clinic. At the completion of day 22, subjects will be reimbursed $20 for time and travel.

## 23.0 Local Number of Subjects

*23.1 Indicate the total number of subjects to be accrued locally.*

Response: 40

*23.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)*

Response: N/A

## 24.0 Confidentiality

*Describe the local procedures for maintenance of confidentiality.*

*24.1 Where and how data or specimens will be stored locally?*

Response: All PHI collected and associated with this study will be kept in a binder designated to each subject and stored in a locked cabinet (in a room that can be locked as well) at the UB OBGYN offices at 219 Bryant St. (Women and Children's Hospital of Buffalo)

*24.2 How long the data or specimens will be stored locally?*

Response: Data will be stored for at least 3 years in accordance with US DHHS E6 GCP guidelines

*24.3 Who will have access to the data or specimens locally?*

Response: Members of the study team approved by the IRB will have access to the data.

*24.4 Who is responsible for receipt or transmission of the data or specimens locally?*

Response: The primary study coordinator will obtain and transmit de-identified data onto the designated electronic database.

*24.5 How data and specimens will be transported locally?*

Response: The study coordinator or PI will have possession of all study materials upon patient visits. This includes transporting data sheets and subject binders. Subject binders will be kept with the research coordinator (or whomever is completing the study visit, as approved study staff) at all times.

## 25.0 Provisions to Protect the Privacy Interests of Subjects

*25.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place*

*limits on whom they interact or whom they provide personal information.*

Response: full disclosure of who may have access to a subject's information is disclosed in the informed consent document and HIPAA Authorization

*25.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.*

Response: A full description of types of information being collected during the study will be disclosed to the subject as outlined in the consent document and during the informed consent process. Subjects will be reminded that their participation is voluntary and that they do not need to provide information/complete questionnaires or procedures that they are not comfortable with and that this will not affect their medical care or relationship with their provider.

*25.3 Indicate how the research team is permitted to access any sources of information about the subjects.*

Response: Subjects will read, understand, and sign a HIPAA Authorization at the time of consent.

## 26.0 Compensation for Research-Related Injury

*26.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.*

Response: Routinely, the Buffalo General Hospital, Erie County Medical Center, Women's & Children's Hospital of Buffalo, Millard Fillmore Hospital, Sisters of Charity Hospital, Strong Memorial Hospital, Highland Hospital and/or the University at Buffalo, State University of New York, or University of Rochester its agents, or its employees do not compensate for or provide free medical care for human subjects in the event that any injury results from participation in a human research project. In the unlikely event that a subject becomes ill or injured as a direct result of participating in this study, they may receive medical care, but it will not be free of charge even if the injury is a direct result of study participation.

*26.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.*

Response: N/A

## 27.0 Economic Burden to Subjects

*27.1 Describe any costs that subjects may be responsible for because of participation in the research.*

Response: There are no costs to subjects for taking part in this study, outside of the cost of routine care.

## 28.0 Consent Process

*28.1 Indicate whether you will be obtaining consent*

Response: Consent will be obtained from all subjects with the capacity to give consent.

*28.2 Describe where the consent process take place*

Response: Consenting will occur in the ED, inpatient unit, or outpatient clinic (Women's Health Clinic at WCHOB). All consenting procedures will occur in a private area.

*28.3 Describe any waiting period available between informing the prospective subject and obtaining the consent.*

Response: Subjects will be able to take reasonable amount of time to consider participation in the study. Subjects may take the consent document home for discussion with family members.

*28.4 Describe any process to ensure ongoing consent.*

Response: Any new information regarding this study that may impact the subject's decision to continue participation in the trial will be communicated to the subject as soon as possible.

*28.5 Describe whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:*

- *The role of the individuals listed in the application as being involved in the consent process.*
- *The time that will be devoted to the consent discussion.*
- *Steps that will be taken to minimize the possibility of coercion or undue influence.*
- *Steps that will be taken to ensure the subjects' understanding.*

Response: Consent will be obtained according to SOP: Informed Consent Process for Research (HRP-090). The PI will confirm the subject's signature, provide a copy of the consent to the subject and store the original in their locked office.

***Non-English Speaking Subjects***

*28.6 Indicate what language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.*

Response: N/A. Only English speaking subjects will be enrolled.

*28.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.*

Response: N/A

***Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)***

*28.8 Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:*

Response: N/A

*28.9 If the research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:*

Response: N/A

***Subjects who are not yet adults (infants, children, teenagers)***

*28.10 Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

Response: N/A

*28.11 For research conducted outside of NY state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition*

*of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response: N/A

*28.12Describe whether parental permission will be obtained from:*

- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.*
- *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*

Response: N/A

*28.13Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.*

Response: N/A

*28.14Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.*

Response: N/A

*28.15When assent of children is obtained describe whether and how it will be documented.*

Response: N/A

***Cognitively Impaired Adults***

*28.16Describe the process to determine whether an individual is capable of consent. The IRB sometimes allows the person obtaining assent to document assent on the consent document and does not automatically require assent documents to be used.*

Response: N/A. Only adults with the capacity to provide consent will be consented.

***Adults Unable to Consent***

*When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent and, where possible, assent of the individual should also be solicited.*

*28.17List the individuals from whom permission will be obtained in order of priority. (e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." The list in the consent template signature section corresponds to the priority list for NYS.*

Response: N/A. Only adults with the capacity to provide consent will be consented.

*28.18For research conducted outside of NY state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response: N/A.

*28.19Describe the process for assent of the subjects. Indicate whether:*

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, an explanation of why not.*
- *Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.*

Response: N/A. only adult subjects (18+ years) will be consented.

*28.20For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.*

Response: N/A

## 29.0 Process to Document Consent in Writing

*If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.*

*(If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach a consent script. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script.)*

*29.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.*

Response: Consent will be documented according to the SOP Written Documentation of Consent (HRP-091).

## 30.0 Drugs or Devices

*30.1 If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.*

Response: For the blinded phase of the study, study medications are housed in the inpatient pharmacy at each respective enrolling institution. Study medication (gabapentin and ondansetron) for the open label phase are stored securely in the UB OB/GYN offices.

*If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:*

*30.2 Identify the holder of the IND/IDE/Abbreviated IDE.*

Response: Thomas Guttuso, Jr., MD

*30.3 Explain procedures followed to comply with FDA sponsor requirements for the following:*

| | *Applicable to:* | | |
|---|---|---|---|
| ***FDA Regulation*** | ***IND Studies*** | ***IDE studies*** | ***Abbreviated IDE studies*** |
| ***21 CFR 11*** | ***X*** | ***X*** | |
| ***21 CFR 54*** | ***X*** | ***X*** | |
| ***21 CFR 210*** | ***X*** | | |
| ***21 CFR 211*** | ***X*** | | |
| ***21 CFR 312*** | ***X*** | | |
| ***21 CFR 812*** | | ***X*** | ***X*** |
| ***21 CFR 820*** | | ***X*** | |

Response: All above applicable FDA requirements have been met for this IND study.