Protocol Outline

Protocol Title: Randomized controlled trial of Glargine versus neutral protamine Hagedorn insulin for the treatment of diabetes mellitus in pregnancy.
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I. Abstract

The national prevalence of diabetes mellitus (DM) and diagnosis of gestational DM in pregnancy has increased over the last 5 years in the United States (1,2). DM has significant risks for both the patient and the fetus in pregnancy including hypertensive disease of pregnancy, congenital anomalies, growth abnormalities, stillbirth, labor complications, preterm delivery, and neonatal complications (3,4). The majority of patients with pregestational DM complicating pregnancy and 15% of patients with gestational DM will require insulin for glycemic control (3,4).

In pregnancy, and at our institution, we have predominantly used neutral protamine Hagedorn (NPH), an intermediate acting insulin. Detemir and glargine may also used if the patient was on these insulins prior to pregnancy. NPH has been available for use since the 1940s and therefore its safety in pregnancy has been well established. Conversely, glargine became available in the US in 2000 and detemir in 2005. In nonpregnant patients, comparisons between long-acting insulin analogues glargine and detemir to NPH have been well studied and shown fewer episodes of hypoglycemia when using long-acting insulin analogues to achieve glycemic control (5,6). Previous randomized control trials (RCTs) support the use of detemir for the management of DM in pregnancy (7,8). In these studies, detemir was found to be noninferior and cause less hypoglycemic episodes in comparison to NPH (7,8). However, there are no RCTs using glargine in pregnancy.

Therefore, we are planning an open-label, noninferiority, randomized study, to compare patients with DM complicating pregnancy to treatment with glargine vs. NPH. Our primary outcome will be the number of patients with hypoglycemic episodes in each group. At Loyola, in the last year, 12% (8/66) of our patients being managed for diabetes mellitus (T2DM, GDMA2) in pregnancy with NPH insulin have had a hypoglycemic episode. We hypothesize, based on previous RCTs comparing detemir and NPH, that the use of glargine in pregnancy compared to NPH will be noninferior and that the rate of hypoglycemic episodes may be reduced with the use of glargine.

II. Background and Significance/Preliminary Studies

Disease background

The national prevalence of diagnosed diabetes mellitus has increased from 9.5% of all US adults in 2016 to 11.3% of all US adults in 2021 (1). As well, the percentage of mothers giving birth that were diagnosed with gestational diabetes mellitus during

their pregnancy increased from 6.0% in 2016 to 8.3% in 2021 (2). Type 2 DM is diagnosed prior to pregnancy by a hemoglobin A1C >=6.5%, fasting blood glucose >=126 mg/dL, random blood glucose >=200 mg/dL with signs or symptoms of type 2 diabetes and/or two-hour blood glucose >=200 mg/dL during the oral 2 hour 75g glucose tolerance test (3). Gestational DM is diagnosed by an abnormal 3 hour 100 g glucose tolerance test in pregnancy with >=2 abnormal values by Carpenter and Coustan criteria (4).

There are many maternal and fetal risks associated with DM in pregnancy, particularly with poorly controlled glycemic control and persistent hyperglycemia. Maternal risks include hypertensive disease of pregnancy, hypoglycemia, diabetic ketoacidosis, preterm delivery, shoulder dystocia, labor complications and cesarean delivery (3,4). Fetal risks include growth abnormalities, congenital abnormalities, still birth and neonatal complications such as hypoglycemia, hyperbilirubinemia, hypocalcemia, respiratory distress syndrome, and NICU admission (3,4). Offspring of mothers with gestational diabetes are more likely to develop obesity and diabetes (4). Patients with diagnosis of gestational DM are also at an increased risk of developing type 2 DM postpartum (4). Prior studies have shown that with strict glycemic control in the treatment of diabetes, these pregnancy outcomes may be improved (3,4). Approximately 15% of patients with gestational diabetes mellitus and the majority of patients with pregestational diabetes mellitus will not be able to achieve glycemic control with diet modification and exercise alone and will eventually require insulin for management (3,4).

Study Agent(s)/Devices Background and Associated Known Toxicities

There is a wide variety of antihyperglycemics available for the management of DM, including oral medications and insulin. Insulin is the preferred hypoglycemic agent during gestation as it is known that insulin does not cross the placenta and interact with fetal glucose metabolism (3,4). Furthermore, dosing can be titrated to achieve glycemic goals. In contrast, oral antihyperglycemic agents are not as predictable in their effect on blood glucose and there is limited data on neonatal outcomes as they do cross the placenta (9,10). Of the various insulin analogues, the medications vary by onset of medication, peak of onset and medication duration. The mechanism of action is generally similar among the various insulins with protracted release of the active insulin dependent on the structure of the insulin analogue (11-13). Insulin acts on cell receptors to increase uptake of glucose into liver, skeletal muscle and adipose tissue (11-13). This may result in hypoglycemia, which can pose both a maternal and fetal risk with coma and fetal acidemia, and thus, one the goals when titrating the dose of insulin to achieve glycemic control is also to avoid hypoglycemic episodes (3-4,11-13).

Hypokalemia is a rare adverse effect of insulin (11-13). Usually mild cases present with muscle pain or cramps, unusual weakness or fatigue, or constipation. Severe cases may result in arrhythmia and worsening of cardiac function. Thus, the use of insulin should be made with caution in the setting of preexisting heart failure and with concurrent use with specific oral antihyperglycemic agents (10,12).

Currently, many facilities differ among use of insulin analogues for management of DM in pregnancy with NPH, glargine and detemir being the most commonly used

analogues for basal insulin. NPH has been available for use since the 1940s and therefore its safety in pregnancy has been well established. Conversely, glargine became available in the US in 2000 and detemir in 2005. NPH is an intermediate-acting insulin with a peak onset of 4-8 hrs from administration and lasting total duration of 14-24 hours (3). Glargine and detemir are long-acting insulins that release insulin up to 24 hours without a peak onset (3). In nonpregnant patients, comparisons between long-acting insulin analogues glargine and detemir to NPH have been well studied and shown fewer episodes of hypoglycemia when using long-acting insulin analogues to achieve glycemic control (5,6). There are recent RCTs comparing detemir and NPH for management of diabetes mellitus in pregnancy showing noninferiority of detemir compared to NPH and in some studies, fewer hypoglycemic episodes with the use of detemir (7,8). Additionally, there are many retrospective studies and meta-analyses comparing glargine and NPH for the management of diabetes mellitus in pregnancy with similar outcomes (14-19). Limitations with these studies have been insufficient power for statistical significance. However, thus far, no randomized studies comparing glargine to other insulins have been completed in pregnancy.

Rationale

Hypoglycemia is a concerning risk of insulin therapy. Prior RCTs have shown noninferiority comparing detemir and NPH for the management of diabetes mellitus in pregnancy, with the longer acting insulin analogue, detemir, having less incidence of hypoglycemic episodes. Therefore, we plan to compare Glargine and NPH and show that the use of it is noninferior and that there may be benefits with the use of Glargine compared to NPH with decreased episodes of hypoglycemia.

III. Study Aims

a. We hypothesize that the use of Glargine in pregnancy will be noninferior to the use of NPH in pregnancy in the achievement of glycemic control in pregnancy.
   Primary outcomes:
   i. To compare the rate of hypoglycemia in patients being treated for diabetes mellitus with NPH vs Glargine insulins.
   ii. To compare to interval of time it takes to achieve glycemic control with the use of NPH vs Glargine insulins.
   iii. To compare patient satisfaction with the use of NPH vs Glargine.
b. We hypothesize that Glargine in pregnancy will be noninferior to the use of NPH in pregnancy in regards to maternal and fetal outcomes.
   Secondary outcomes:
   i. To compare the rate of LGA in patients being treated for diabetes mellitus with NPH vs Glargine insulins.
   ii. To compare the rate of shoulder dystocia in patients being treated for diabetes mellitus with NPH vs Glargine insulins.

I. Administrative Organization

a)

b) The study will be conducted at Loyola University Medical Center and patient interaction will occur in the both the Loyola Outpatient Center as well as Labor and Delivery. Data will be collected on the Loyola REDCaps (Research Electronic Data Capture), server and analyzed by biostatisticians at Loyola University Chicago Health Sciences Campus Center for Translational Research and Education. All hard copy data will be kept in a locked cabinet in a locked office. All electronic data will be kept in a secure Loyola research server. Data and patient identifiers will be destroyed when the project is completed. The PIs will have access to the PHI. The data will be used for data analysis, presentation and publication.

IV. Study Design

This is an open-label, noninferiority, prospective randomized study. Patients will be randomized to either be treated with NPH insulin for management of diabetes mellitus in pregnancy, or with Glargine insulin. We will include all pregnant patients managed by the Maternal Fetal Medicine team at Loyola University of Medical Center that have pregestational Type 2 Diabetes Mellitus or Gestational Diabetes Mellitus requiring insulin.

Inclusion criteria includes all patients with the diagnosis of gestational diabetes mellitus requiring insulin or type 2 diabetes mellitus requiring insulin, at least 18 years old, singleton and multiple gestation, that have established prenatal care by 14 weeks gestation and started on insulin by 34 weeks gestation. Patients excluded from the study will be those under the age of 18 years old, who are unable to consent, have an allergy to insulin, are controlled only with diet modification or the use of oral antihyperglycemics, have diagnosed pregestational Type 1 diabetes mellitus, or receive insulin through an insulin pump.

The primary objective of this randomized controlled trial is to compare the rate of hypoglycemia in patients being treated for Diabetes Mellitus with Neutral Protamine Hagedorn (NPH) insulin vs Glargine insulins. Primary outcomes will include episodes of hypoglycemia diagnosed by blood glucose reading <60 mg/dL. Secondary outcomes will be large for gestational age defined by neonatal birth weight >=90% for gestational age and shoulder dystocia at time of delivery (diagnosed by delivering provider).

Sample sizes of 64 in Group NPH and 64 in Group Glargine will achieve a 90.32% power to detect a difference of 0 when the non-inferiority difference is 0.2. The reference group proportion is 0.18. This reference group rate of hypoglycemia was based on the referenced meta-analysis below. The treatment group proportion is assumed to be 0.38 under the null hypothesis. The power was computed for the case when the actual treatment group proportion is 0.18. The test statistic used is the one-sided Z test (unpooled). The significance level of the test is 0.05. Below is a figure (figure 1) showing the equal sample size per group with varying level of non-inferiority margin from 10% to 20%. With an Anticipated 20% dropout rate, 80 subjects should be enrolled in each group 2, to obtain final group sample sizes of 64 and 64, respectively.

Additional information collected will be patient demographics (race, ethnicity, marital status, insurance type, social determinants), diagnosis of polyhydramnios made antepartum, total pregnancy weight gain, development of preeclampsia, progression of retinopathy, intrauterine fetal demise, gestational age at delivery, mode of delivery, birth weight of neonate at delivery, Apgar score at 1 and 5 minutes, presence of congenital malformations, neonatal intensive care unit admission, neonatal hypoglycemia (<40 mg/dL during first 24 hours of life), respiratory distress syndrome (requiring supplemental oxygen with weaning difficulties), hyperbilirubinemia and neonatal death.

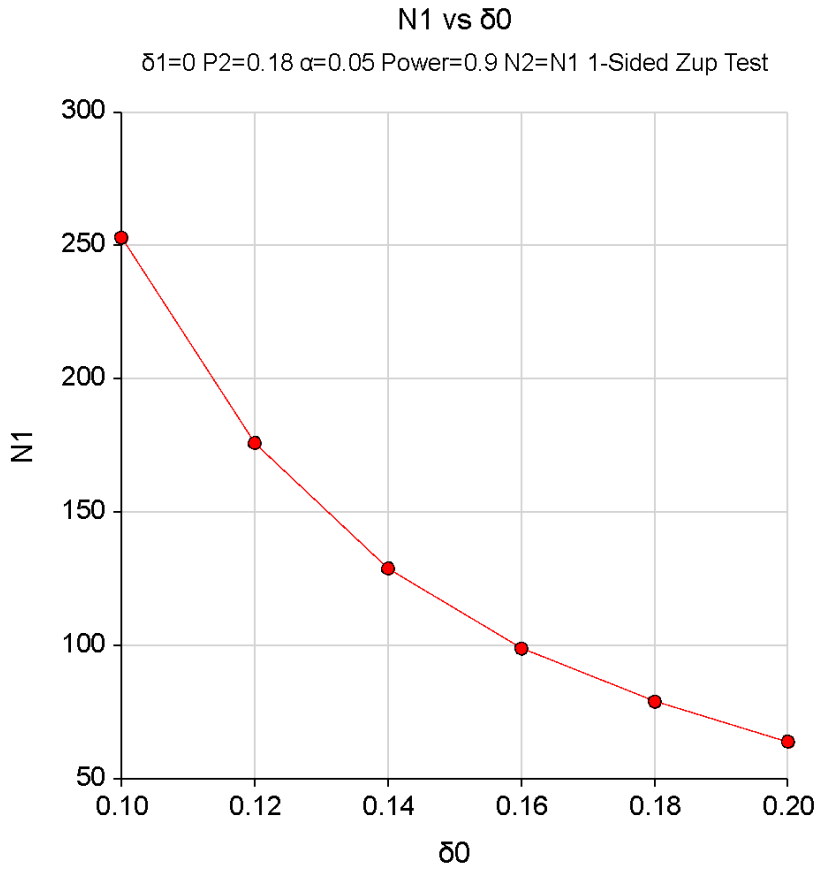

Figure 1. Power analysis for non-inferiority

V. Study Procedures

Patients will be recruited when they present to Loyola University Medical Center Maternal Fetal Medicine for consultation for management recommendations of Diabetes Mellitus in pregnancy. Diagnosis of type 2 diabetes mellitus will be made prior to pregnancy with at least a hemoglobin A1C >=6.5%. The diagnosis of gestational diabetes mellitus will be made with a routine 3 hour glucose tolerance test with >=2 abnormal values by the Carpenter and Coustan Criteria (4). Patients diagnosed with gestational diabetes mellitus will be initially treated with diet modification and given referral to diabetic nutrition education. If patients fail to establish adequate glycemic control with

diet modification and exercise alone and require insulin therapy, they will then be eligible for the study and randomized accordingly. Patients will be recruited at these visits and consented by one of four Maternal Fetal Medicine physicians in writing (Appendix A).

Patient will be randomized to either receive Glargine or NPH. Randomization to either group will be completed through Loyola REDCap. Patients will be started on weight-based dosing of insulin with adjustments to the dose based on clinical judgement by Maternal Fetal Medicine physician group. Either Glargine or NPH will be ordered through electronic prescription to the patient's requested pharmacy and cost of medications will be the patient's responsibility after insurance coverage is applied. Patients and Providers will not be blinded to which form of insulin the patient will be treated with. Patients in both groups will also be prescribed short-acting insulin in the form of Aspart or Lispro as needed. No additional funding will be required for completion of this study. For patients presenting to LUMC MFM for consultation that are already started on insulin, they will be offered to participate in the study and be randomized to the control or intervention groups if they meet the inclusion criteria. All patients will receive insulin teaching from a registered nurse and referred to the LUMC Diabetic Education classes if they have not yet completed the course (Appendix B). No additional funding will be required for completion of this study.

All patients will be responsible for monitoring their blood glucose with a glucometer at home. They will be prescribed at minimum, a glucometer, lancets, and glucose test strips. Patients will monitor their blood glucose at least four times a day – fasting in the morning, 2 hours after breakfast, 2 hours after lunch and 2 hours after dinner. All patients will be registered with the MyLoyola Glucose Flowsheet in their EPIC electronic medical record and be asked to record their blood glucose values through the phone app using their personal mobile device. Every 2 weeks, the patient's blood glucose log will be reviewed by a Maternal Fetal Medicine physician, remotely or in person, and will expect dose adjustments as needed. Insulin doses will be adjusted to maintain >50% fasting blood glucose values <95 mg/dL and >50% 2 hour postprandial blood glucose values <120 mg/dL. Insulin doses will also be adjusted to avoid hypoglycemic episodes with blood glucose values <60 mg/dL and for symptomatic hypoglycemia with blood glucose values <80 mg/dL. Hemoglobin A1C will be collected in the first trimester prior to initiation of insulin and third trimester prior to delivery.

Additionally, serial growth ultrasounds will be performed every 4 weeks after anatomic survey, weekly biophysical profiles for antenatal fetal surveillance starting at 32 weeks and an induction of labor offered at 39 weeks or earlier as indicated. Data will be obtained from the patient's electronic medical record and patient satisfaction by administered DTSQ (Appendix C). Entire protocol is outlined in the study schema below (Figure 2).

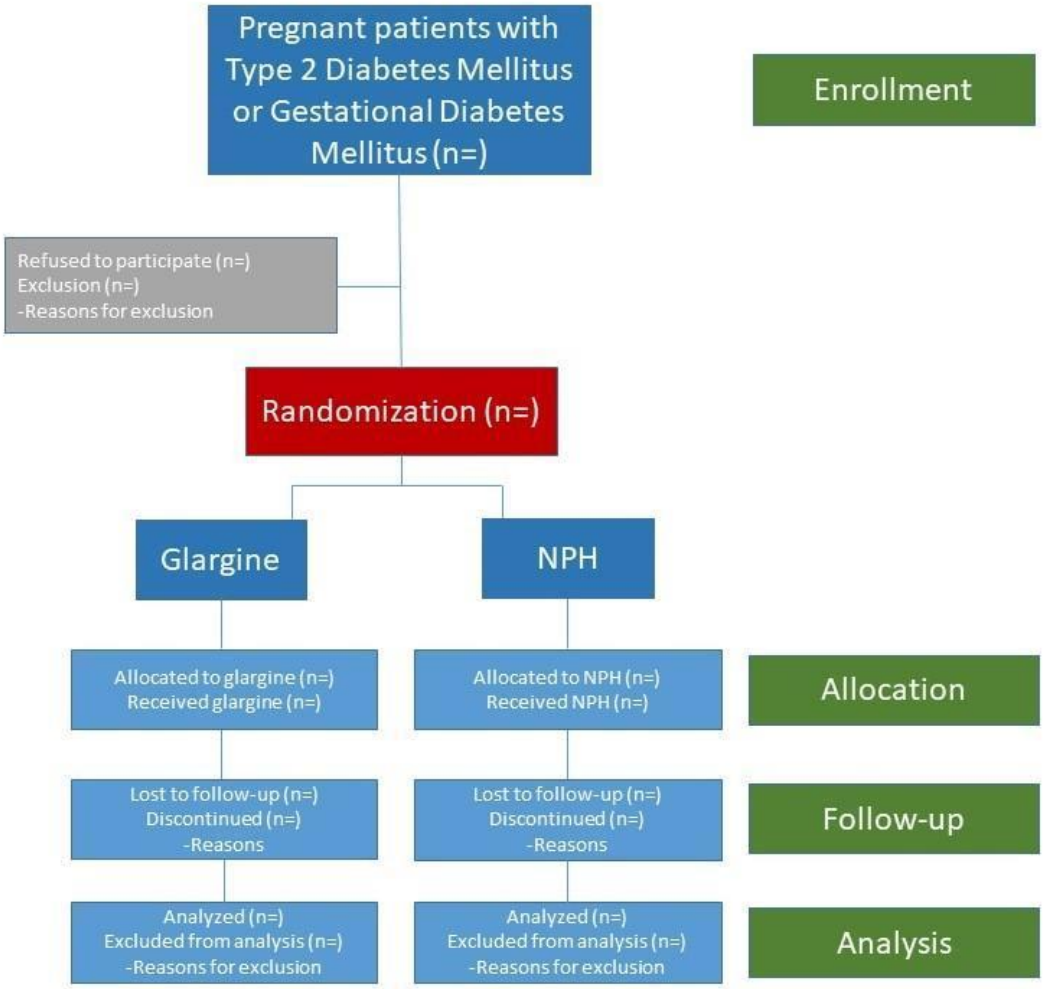

Figure 2. Study Schema

Pregnant women are considered a vulnerable population. As the condition of interest is a pregnancy-related and specific condition, it is unavoidable to exclude pregnant women from this research study. However, all risks to this vulnerable population will be minimized as all forms of insulin used in this study, NPH, Glargine, Aspart and Lispro are standard care for management of diabetes mellitus (3). Thus, the use of Glargine in the intervention group will not be a deviation from standard of care for the medical diagnosis. There are minimal risks to either medication used, most common risk known is hypoglycemia (10,11). Furthermore, neonates are considered a vulnerable population. We will be collecting data on neonatal rates on NICU admission to determine if there are any adverse effects of either insulin to the neonates. All risks of this vulnerable population will be less than minimal risk as insulin does not cross the placenta to interact with the neonate and the greatest risk would be fetal acidemia from severe maternal hypoglycemia or severe neonatal hypoglycemia seen with poor glycemic control (3). Instructions will be provided to patients on how to manage hypoglycemic episodes (Appendix D).

Being enrolled in this study will not change patients' clinical care in regards to antepartum course or delivery decisions. Their intrapartum management will not be different in any way. Regardless of randomization, the management will not be different in either arm apart in regards to insulin dose adjustments.

The potential benefit will be decrease rates of hypoglycemia as seen in prior retrospective studies. All efforts will be taken to minimize the risks associated with this study and the risks overall are considered minimal; therefore, the risk to subjects is reasonable compared to the benefit to patients and to society in general.

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

a) Patient voluntarily withdraws from treatment (follow-up permitted);
b) Patient withdraws consent (termination of treatment and follow-up);
c) Patient is unable to comply with protocol requirements;
d) Patient experiences an allergic reaction to the insulin that makes continuation in the protocol unsafe;
e) Treating physician judges continuation on the study would not be in the patient's best interest;
f) Lost to follow-up;
    a. If a research subject cannot be located to document outcomes after a period of 4 weeks, or two missed appointments, the subject may be considered "lost to follow-up." All attempts to contact the subject by telephone/voicemail or MyLoyola inbox messages will be documented.
g) The study is stopped.

VI. Safety Monitoring Plan

Drug information on Insulin neutral protamine Hagedorn (NPH) also known as Isophane insulin (11, 20)

- Other brand names for the drug: Humulin N, Novolin N
- Classification - type of agent: Intermediate-acting insulin
- Mode of action: increases cellular uptake of glucose in the liver, adipose tissue and skeletal muscles. Protamine-splitting enzymes and macrophages invade the subcutaneous tissue and dissolve the NPH insulin suspension to facilitate the protracted release of insulin. The onset of action is in 1-3 hours with peak effect in 4-8 hours. Total duration of the medication is 14-24 hours. It is metabolized by the liver and excreted in urine.
- Protocol dose: as prescribed by provider
- Route of administration for this study: subcutaneous
- Incompatibilities: none. Concern with synergistic properties when used with Long-acting insulin.
- Availability: commercially available, on formulary
- Side effects: nocturnal hypoglycemia, fasting hyperglycemia, weight gain, peripheral edema, hypokalemia, lipodystrophy, or hypersensitivity/allergic reaction.

- Pregnancy: Poorly controlled diabetes mellitus during pregnancy is a cause of fetal complications, including congenital anomalies. Insulin therapy can reduce the risk of those complications.

Drug information on Glargine (12, 21):

- Other brand names for the drug: Lantus, Lantus SoloStar, Toujeo, Basaglar, Semglee, Rezvoglar
- Classification - type of agent: Long-acting insulin
- Mode of action: increases cellular uptake of glucose in the liver, adipose tissue and skeletal muscles.
- Protocol dose: as prescribed by provider
- Route of administration for this study: subcutaneous
- Incompatibilities: none. Concern with synergistic properties when used with other long-acting insulin or intermediate-acting insulin. Concerns with taking medication with pioglitazone or reosiglitazone. Caution with use in patients with liver disease, kidney disease, heart failure or other heart problems.
- Availability: commercially available, on formulary
- Side effects: hypoglycemia, weight gain, hypokalemia, lipodystrophy, or hypersensitivity/allergic reaction.
- Pregnancy: Pregnancy effects of insulin glargine are anticipated to be similar to those of other insulins #1095 (poorly controlled diabetes mellitus during pregnancy is a cause of fetal complications, including congenital anomalies. Insulin therapy can reduce the risk of those complications), which do not increase the risk of congenital anomalies.

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention. Adverse event data collection and reporting will be done to ensure the safety of subjects who will enroll be enrolled in thus study. Adverse events will be reported in a routine manner at scheduled times during the trial. Additionally, certain adverse events will be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

c) The adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
d) Any abnormal laboratory values have returned to baseline;
e) There is a satisfactory explanation other than the study drug for the changes observed; or
f) Death.

Steps to determine if an adverse event requires expedited reporting:

1. Identify the type of adverse event.
2. Grade the adverse event.

a. Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
b. Moderate (grade 2): the event causes discomfort that affects normal daily activities.
c. Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
d. Life-threatening (grade 4): the patient was at risk of death at the time of the event.
e. Fatal (grade 5): the event caused death.

3. Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
    a. Definite – The AE *is clearly related* to the study treatment.
    b. Probable – The AE *is likely related* to the study treatment.
    c. Possible – The AE *may be related* to the study treatment.
    d. Unrelated – The AE *is clearly NOT related* to the study treatment.
4. Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the age. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in
    a. The current known side effects listed under the "Drug Information" on the medication (10,11)
    b. The drug package insert;
    c. Web-source Reprotox (18,19)

For routine reporting, all other adverse events, such as those that are expected or are unlikely or definitely not related to the study participation – are to be reported annually as part of regular data submission. For expedited reporting, the Principal Investigator will be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug. The Loyola University Medical Center IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO). The following events meet the definition of UPR:

a) Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
b) Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
c) Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
d) Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
e) Any breach in confidentiality that may involve risk to the subject or others.

f) Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

II. Analysis Plan

This is a randomized controlled noninferiority trial of pregnant women with the primary outcome being the rate of hypoglycemic events. The goal is to show that Glargine is at least almost as good as NPH in pregnant women. The null hypothesis therefore is that both Glargine and NPH have the same effect on rate of hypoglycemic events in pregnant women. If we reject this hull hypothesis by means of a p-value or a confidence interval, it will simply mean that Glargine and NPH have different effects on rate of hypoglycemic events in pregnant women. Therefore, we intend to summarize baseline characteristics for all patients recruited for the study as well as per randomized group separately. Continuous variables will be reported as means (with standard deviation) while categorical variables will be reported as counts (with percentages). Chi-square test of associations (or Fisher's exact test) will be used for categorical variables while T-test or a non-parametric equivalence will be used to compare continuous variables between the two groups. 95% Confidence Intervals will also be recorded for continuous variables. No adjustment will be made for multiple comparisons for the secondary aims. In the case where a multiple testing scenario will be deemed necessary, standard adjustments techniques such as Bonferroni correction will be used. Intent-to-Treat Analysis will be performed, that is, all patients will be analyzed in the group they were originally randomized to whether they completed the study in their group or not. In an effort to avoid effect of patients' eventual poor adherence (although it is estimated to be minimal here) on rate of hypoglycemia, a per-protocol analysis will be attempted, and results will be summarized. Potential impact of any sub-group on the rate of hypoglycemia will also be analyzed. Since the blood glucose will be recorded four times a day, an exploratory analysis may be performed to study the change over time of blood glucose. A mixed model may be attempted on this front.

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