1. OVERVIEW

1.1 Study Overview

Offspring of mothers with pre-existing diabetes mellitus (DM) or gestational DM (GDM) have an increased risk of obesity in childhood. Moreover, GDM is associated with an increased maternal risk of type 2 diabetes. What has not been established is the risk of childhood obesity and metabolic disorders or maternal risk of disorders of glucose metabolism (diabetes, impaired fasting glucose, impaired glucose tolerance) and other cardiovascular risk factors (dyslipidemia, increased abdominal adiposity (girth), elevated blood pressure (BP)) along the continuum of glucose to levels diagnostic of diabetes. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Follow-up Study will use its unique resource, a cohort of women and their offspring who were recruited into the HAPO Study in 2000-2006, to address these questions. The overall ***hypothesis*** of the HAPO Follow-Up Study is:

> ***Hyperglycemia in pregnancy, less severe than overt DM, is independently associated with increased risk of adverse childhood and maternal outcomes 8-12 years later.***

The HAPO Study was an observational epidemiologic investigation aiming to clarify associations of levels of glucose intolerance during pregnancy and risk of adverse outcomes and to derive internationally acceptable criteria for the diagnosis and classification of GDM. The underlying hypothesis was that hyperglycemia in pregnancy, less severe than overt diabetes, is independently associated with increased risk of adverse maternal, fetal and neonatal outcomes. The HAPO Study examined glucose tolerance in a large, multinational, multicultural, racially diverse cohort of women in the third trimester of gestation with medical caregivers and participants "blinded" to the status of glucose tolerance. A common protocol and data collection instruments, uniform training of personnel, and central laboratory for analyses were used. HAPO demonstrated continuous associations between increasing levels of maternal glucose and each primary and secondary study outcome. Based upon HAPO Study results, a consensus panel formulated new criteria for the diagnosis of GDM.

In HAPO, higher levels of maternal glucose were independently associated with increased frequency of birthweight, cord serum C-peptide, and infant adiposity (infant percent body fat or sum of skinfolds) above the 90th percentile. These same neonatal outcomes are risk factors for

obesity and metabolic disorders in childhood and later life, but primarily in offspring of diabetic mothers. The nature of the associations and magnitude of risk associated with increasing levels of maternal glycemia below those diagnostic of diabetes, including mothers who would be newly diagnosed with GDM based upon the new IADPSG criteria, are not well characterized. A HAPO Follow-up Study is uniquely positioned to address these important questions given the breadth of maternal and neonatal phenotype data collected across multiple ethnic groups.

The HAPO Follow-up Study is to be accomplished with high quality standardized data collection on 7,000 women and their children from 10 of the original 15 HAPO field centers. The HAPO Follow-up Study includes a Clinical Coordinating Center (CCC), Data Coordinating Center (DCC), and Laboratory Coordinating Center (LCC) all located in Chicago and funded by the US National Institutes of Health through a cooperative agreement.

1.2 Summary of Tasks

Key study tasks in the HAPO Follow-Up Study are to:

- Develop a common protocol and data collection instruments.
- Train field center personnel for standardized data collection.
- Recruit and enroll 7,000 women and children who participated in the original HAPO Study at 10 of the 15 field centers.
- Complete an exam on each child, including completion of a questionnaire, measurement of height, weight, waist and mid-arm circumference, skinfolds, body size and fat measures with the BOD POD, blood pressure, pubertal assessment, and completion of an OGTT with collection of blood for fasting measures of glucose, insulin/C-peptide, lipids, and collection of blood samples at 30, 60, and 120 minutes for measurement of glucose and insulin/C-peptide, and collection of additional blood samples for measurement of A1c, hsCRP, and DNA (on those who provide consent).
- Complete an exam on each mother, including completion of a questionnaire, measurement of height, weight, waist and hip circumference, body size and fat measures with the BOD POD, blood pressure, and collection of fasting blood samples for glucose, insulin/C-peptide, lipids, and collection of glucose at 120 minutes following a 75 g glucose load, and collection of additional blood samples for measurement of A1c, and DNA (on those who provide consent).

- Edit and enter all collected data into the REDCap web-based data entry and data base management system.
- Carry out quality control of all data collection procedures to ensure that all data are being collected in a consistent and reliable fashion.

1.3 HAPO Follow-Up Study Timeline

The HAPO Follow-Up Study is to be completed in four phases. Phase I was a development and planning phase lasting 11 months from July 1, 2010 to May 31, 2011. Phase I was devoted to development of a grant application for funding the Follow-Up Study, including completion of the Protocol and Manual of Operations (MOO); development of data collection forms; preparation of data entry screens for field center entry of study data into the REDCap web-based data management system; planning of the Central training curriculum; planning of quality control procedures for field centers; and planning of detailed Data Coordinating Center procedures for quality control and data management.

Phase II commenced at the time the study was funded. Phase II is to last approximately 6-9 months and includes needed revisions to the Protocol, Manual of Operations, and data collection forms, based on review group recommendations and recommendations of the Observational Study Monitoring Board; translation and back-translation of forms, questionnaires, and other documents translated locally from English into other languages; finalization of quality control procedures for field centers; development of a Laboratory Coordinating Center quality control system; development of detailed Data Coordinating Center procedures for quality control and data management; finalization of plans and materials for Central training; Central training; completion of a Dry Run in each field center of all study procedures, except the child OGTT, its review, any needed corrective action, and Coordinating Center and Executive Committee approval to begin field work.

All field work is to be completed during the 36 – 39 months of Phase III, and all laboratory analyses of blood samples by the end of Phase III, or shortly thereafter, to permit preparation of the final data set and undertaking of data analyses in Phase IV.

Phase III is also devoted to entry of data by field centers and the Laboratory Coordinating Center; monitoring flow of data from field centers to the Data Coordinating Center, with

appropriate quality control; monitoring recruitment progress against recruitment milestones; monitoring representativeness of those agreeing to participate; monitoring activity of the Laboratory Coordinating Center, including flow of blood samples from field centers, flow of sample results to the Data Coordinating Center, and quality control of laboratory analyses; management of data received from field centers and the Laboratory Coordinating Center by the Data Coordinating Center, with ongoing quality control; retraining field center personnel as needed; and preparation of interim reports on data quality and Study progress.

Phase IV, which lasts 12-15 months, is devoted to final data clean-up and statistical analysis of study data, and to preparation of reports for oral presentation and publication.

1.4 Field Center Preparation for the HAPO Follow-up Study

There are a number of issues and questions that HAPO Study field centers will need to consider as they prepare for the HAPO Follow-Up Study. These are questions that need to be addressed for successful implementation of the HAPO Follow-Up Study Protocol and procedures. Although this manual describes in detail procedures to be used for all aspects of data collection, there are many aspects that cannot be prescribed and for which each field center needs to devise methods or procedures. The following list of items is an effort to be comprehensive. Additional items may be identified after implementation of the Study begins. **Note:** Each field center should be prepared to answer these questions at the time their Research Staff attend the Central training session. In addition, these questions will be discussed during the pre-enrollment Dry Run site visit at each field center.

1. How will field centers make contact with their original HAPO participants for recruitment to the HAPO Follow-Up Study? Each field center will need to devise its own method of contacting and recruiting women into the study, based on the information collected at the time of enrollment in HAPO.

2. What days of the week can exams be conducted? Can exams be conducted during weekdays and on weekends, or only on weekends except for school holiday periods? How will field centers ensure adequate staff are available if there are only 1 or 2 exam days per week for much of the year?

3. Are there any other studies being conducted at your field center that could make a woman ineligible for participation in the HAPO Follow-Up Study? A list needs to be prepared, and regularly updated. This list should identify studies that a woman or child who is eligible for the HAPO Follow-Up Study should not participate in, because participation would interfere with HAPO Follow-Up Study protocol and procedures. Such studies will need to be reviewed on a case by case basis to determine which, if any, would preclude participation in the Follow-Up Study.

4. When a woman is being recruited for participation in the HAPO Follow-Up Study, she needs to be given standardized and comprehensive information about the study – a template for that purpose has been prepared. She should also be given information on the important findings of the original HAPO Study – a template has been prepared, and thanked for her for her participation in HAPO. Each field center will need to modify the templates as appropriate to present to their HAPO participants. The information presented at your field center should be comparable to the information contained in the consent documents for your field center.

5. Each field center will need to have some specific facilities available for the HAPO Follow-up Study. Are the following available at your field center?
    a. A desktop or notebook computer for data entry with a high-speed Internet connection. Data entry will be done at each field center using Research Electronic Data Capture or REDCap, a secure web-based software package for data entry and management, developed for use as part of the CTSA – Clinical & Translational Science Awards. Your field center will need to have a specific location dedicated to data entry, so that all HAPO Follow-Up Study forms ready for data entry can be brought to a specific location for data entry. It is preferable that data forms be stored in a location close to the computer where the data will be entered.
    b. Space for storage of supplies. Phlebotomy tubes, specimen storage vials, glucose test bottles for the child and maternal OGTT, laboratory freezer boxes, and polyurethane shipping boxes will be sent to each field center.
    c. Space for storage of HAPO Follow-Up Study participant files and forms. A HAPO Follow-Up Study file should be prepared for each participant following agreement to participate. All forms completed for the mother and her child should be stored in her HAPO file folder. In addition, blank copies of forms should be available.

d. Each field center must have a centrifuge (refrigerated if possible), a –20° C or colder freezer (-70 or -80 is preferred) for storage of blood samples, and access to dry ice for shipment of specimens. The freezer must have a backup power supply in the event of a power outage, or an alarm system for notification of freezer failure. A backup procedure for maintaining specimens in the frozen state should also be available. The freezer must not be of the automatic defrost type.

5. Where will the mother and child visits, including completion of questionnaires, measurement of blood pressure, height, weight, the BOD POD and pubertal assessments, drawing of blood samples, and administration of the mother and child OGTTs be performed and how will the visit be arranged or scheduled? How will you keep track of appointments for this visit?

6. Where will the blood and urine samples be processed at your field center?

7. All blood and urine samples and storage vials must be stored in a –20° C or colder freezer

   (-70 or -80 is preferred). Where will these be stored in your field center?

8. For several of the procedures involved in data collection for the HAPO Follow-Up Study, it is desirable that more than one person receive training. For example, it would be helpful if more than one person was trained in use of the BOD POD and in the measurement of waist circumferences, so that a backup is available in the instance where the Research Nurse is not available. It is also important in the measurement of waist circumference, for example, that the person practices this skill frequently to maintain an acceptable level of performance. Who will be the backup to the Research Nurse at your field center?