Computer Automation for the Diagnosis and Management of Childhood Type 2 Diabetes: A Randomized Clinical Trial

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Study Protocol

C.3.1 Expand and modify an existing computer-based decision support system (CHICA), to identify those children age 10 and older who are at increased risk for type 2 diabetes, to provide pediatric physicians guidelines to screen for the condition, and to coordinate the diagnosis and long-term management of the condition (Aim 1).

Currently the CHICA system is actively utilized at four pediatric primary care practices affiliated with the Indiana University Medical Group-Primary Care (IUMG-PC) practice network – Wishard Pediatric Primary Care, Pecar Health Center, Blackburn Health Center, and Forest Manor Health Clinic. These will be the four clinic sites utilized for our study. Two of these clinics will function as an intervention group and two will function as the control group.

During phase one of this project, we will make several additions and enhancements to the existing CHICA system within these clinic sites. Specifically, rules will be written for the addition of screening questions to the pre-screener form and diagnosis instructions will be programmed for the physician worksheet. Additionally, we are proposing several technical enhancements to the current CHICA system including automated physician order generation and automated reminder phone calls to patients. This technical work will take place in year one of the project, and based on our past experience, we expect this work to take less than 12 months to complete.

C.3.1.1 Program the CHICA Type 2 Diabetes Module
The overall outline for the CHICA type 2 Diabetes Module that will be programmed into the CHICA system is provided in Figures 1 and 2 below.

Information with regard to family history of type 2 diabetes, race/ethnicity, and maternal history of gestational diabetes will be gathered for every patient, regardless of age, by asking these questions of parents on the pre-screener form (Figure 1, Box 1). This data will then be utilized at a later point by the CHICA system when a child is age 10 or older and presents to the clinic. Data regarding the child's BMI at that time will be analyzed by the CHICA system (Figure 1, Box 2). If the child's BMI is greater than the 85th percentile (Figure 1, Box 3), a prompt will appear on the provider worksheet asking the clinician whether the child has any symptoms or conditions associated with insulin resistance (Figure 1, Box 4). This information along with the data gathered previously from the pre-screener form will be analyzed to determine whether the child has 2 or more risk factors for the development of type 2 diabetes (Figure 1, Box 5). If at least 2 risk factors are present, then an automated physician order will be generated for a FPG and HbA1C (Figure 1, Box 6). Patient educational material will be printed out and provided to the family regarding the importance of screening for type 2 diabetes and instructions for the blood test (Figure 1, Box 6). The CHICA system will also recommend that the patient be scheduled for a follow-up visit for the same day as the lab draw occurs, (Figure 1, Box 6) and the patient will receive a CHICA generated reminder telephone call about the lab testing (with instructions for fasting) and follow-up appointment (Figure 1, Box 7).

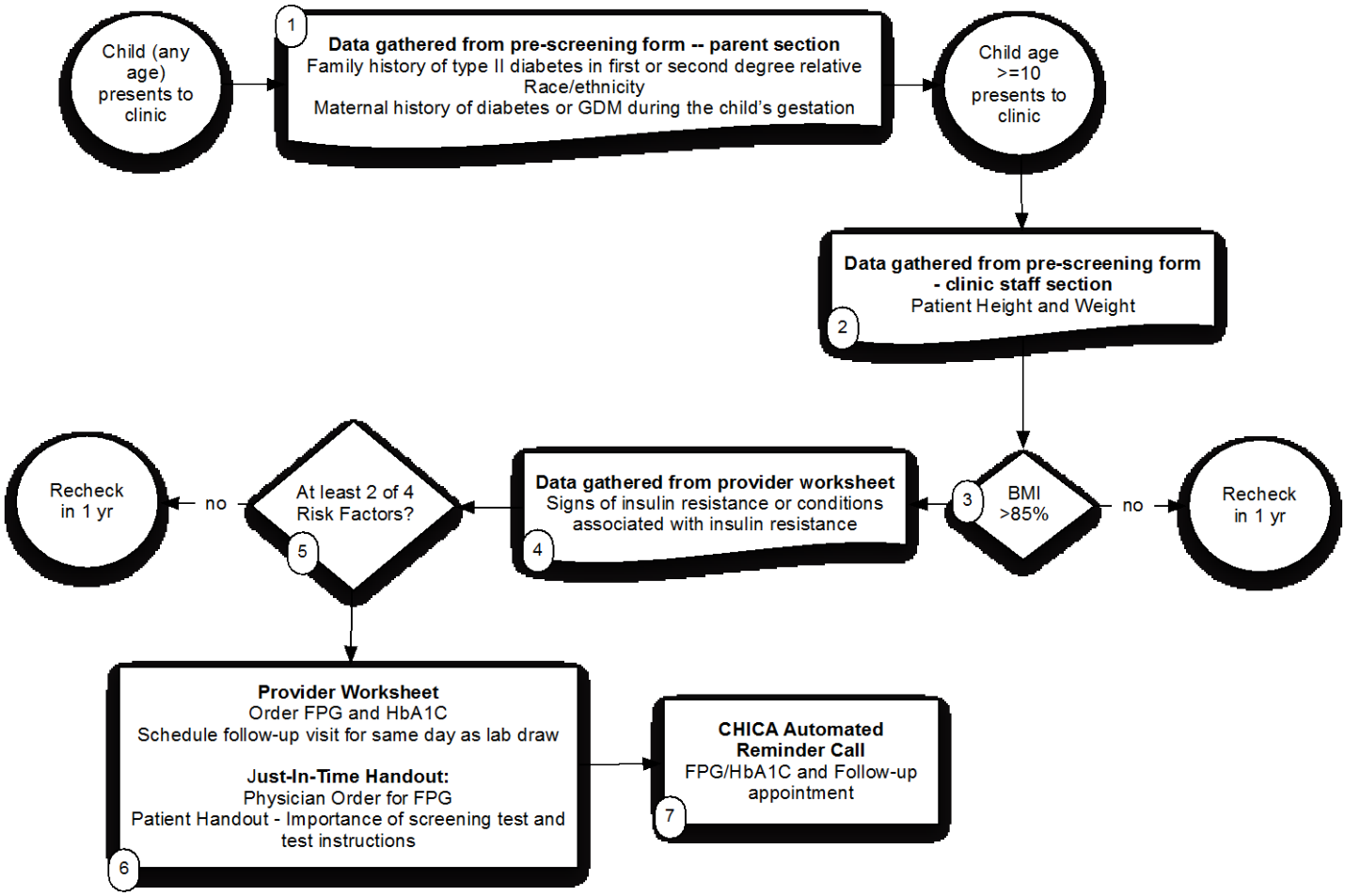

Figure 1. CHICA Type 2 Diabetes Module: Screening in Pediatrician's Office

At the follow-up appointment if FPG is greater than 125 or HbA1C is greater than or equal to 6.5% (Figure 2, Box 1), a prompt will appear on the physician worksheet instructing the physician to refer the patient to pediatric endocrinology, and a referral will be automatically faxed to endocrinology (Figure 2, Box 9). At this time a page to the pediatric endocrinology doctor on call will be initiated automatically by the CHICA system so that the pediatrician can discuss the need for further work-up or immediate referral in the case of symptoms requiring emergent treatment. Additional work-up will be directed by the pediatric endocrinologist (Figure 2, Box 10).The CHICA system will generate an automated reminder telephone call to the patient regarding their scheduled appointment with pediatric endocrinology (Figure 2, Box 11). Following the appointment with endocrinology, feedback regarding management plans will be provided to the pediatrician from the endocrinologist through a structured letter that was generated and faxed by the CHICA system (Figure 2, Box 12). This faxed letter will be received directly by the CHICA system, digitally interpreted, and the data will be automatically deposited into CHICA for display on the provider worksheet at the patient's next appointment with their pediatrician (Figure 2, Box 13).

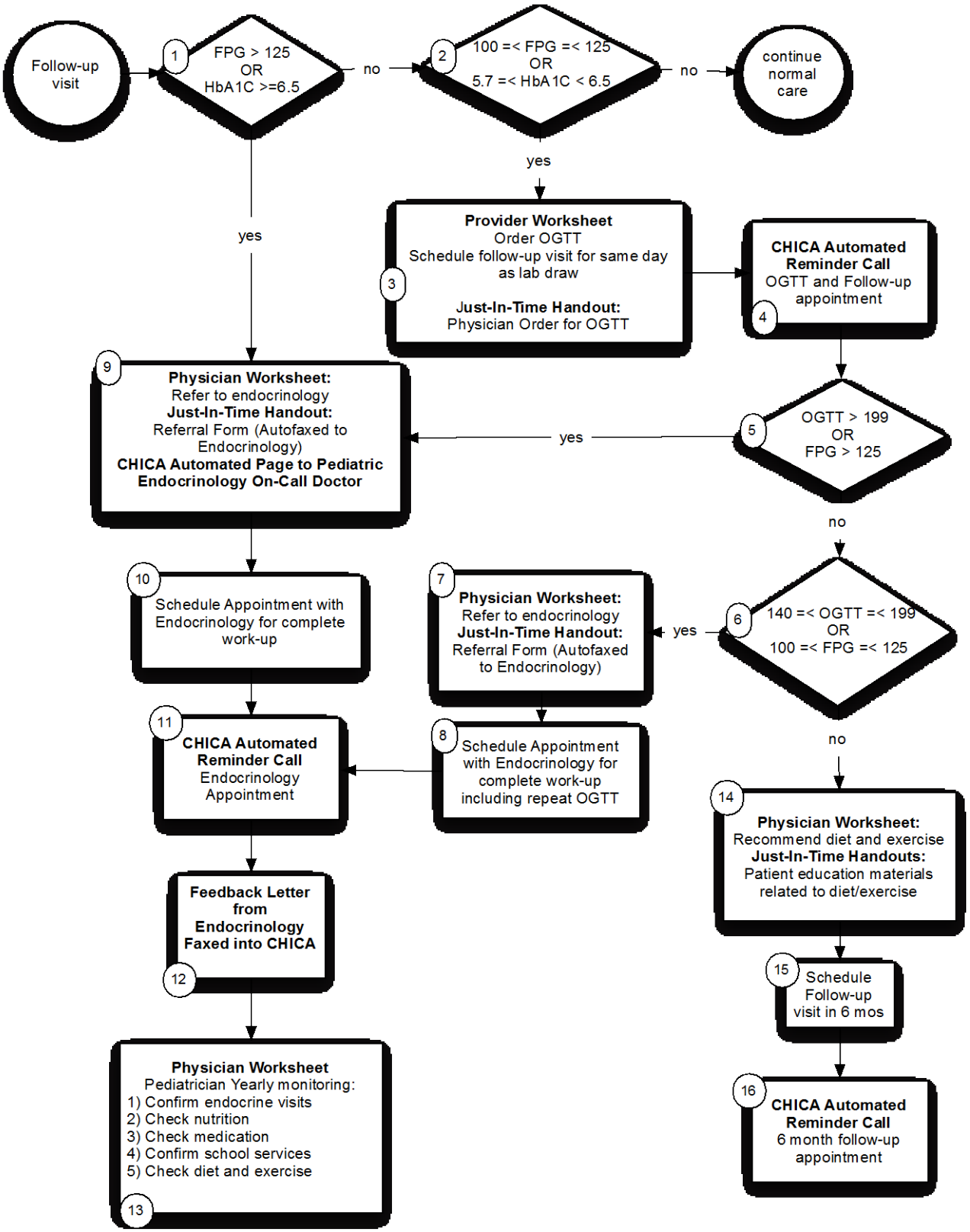

Figure 2: CHICA Type 2 Diabetes Module: Diagnosis and Management

If a child's initial FPG is between 100 and 125 or HbA1C is between 5.7 – 6.4%, then an automated physician order will be generated for an OGTT (Figure 2, Box 3). The CHICA system will also instruct that the patient be scheduled for a follow-up visit for the same day as the lab draw occurs (Figure 2, Box 3), and the patient will

receive a CHICA generated reminder telephone call about the lab testing (with fasting instructions) and follow-up appointment (Figure 2, Box 4). If the OGTT is indicative of diabetes (OGTT > 199) (Figure 2, Box 5), then a prompt will appear on the physician worksheet instructing the physician to refer the patient to pediatric endocrinology, and a referral will be automatically faxed (Figure 2, Box 9). In addition, a page to the pediatric endocrinology doctor on-call will be initiated automatically by the CHICA system so that the pediatrician can discuss the need for further work-up or immediate referral in the case of symptoms requiring emergent treatment. If the OGTT is indicative of pre-diabetes (OGTT between 140 and 199) (Figure 2, Box 6), additional work-up, including a repeat OGTT, will be directed by the pediatric endocrinologist (Figure 2, Box 8).Once again automatic patient reminder telephone calls will be initiated, and feedback letters from endocrinology will be faxed directly into the CHICA system and available to the pediatrician at the patient's next appointment (Figure 2, Box 10-13).

If the OGTT is normal (Figure 2, Box 6) then the pediatrician will be prompted on the physician worksheet to provide the patient with diet and exercise recommendations, and just-in-time educational handouts will be generated for the patient related to these topics (Figure 2, Box 14). The pediatrician will be alerted that these children are at high risk for developing type 2 diabetes due to risk factors and history of an abnormal FPG or HbA1C, and deserve more frequent follow-up. The CHICA system will instruct that the patient be seen again within 6 months (Figure 2, Box 15). At that time, they will have follow-up lab tests performed (fasting glucose, HbA1C, and referral to pediatric endocrinology if they meet the criteria outlined above). The patient will receive a CHICA generated reminder telephone call about this 6 month follow-up appointment (Figure 2, Box 16).

C.3.1.2 Technical Enhancements

A new capability will be added to the CHICA system in the form of automated reminder telephone calls to patients for return laboratory testing and follow-up appointments. CHICA software will initiate a programmatic request to a third party Voice over IP (VoIP) based auto dialer software. The auto dialer will initiate the call from a preconfigured list of telephony service provider(s) such as Skype (www. Skype.com) or others using the industry standard Session Initiation Protocol (SIP). We will evaluate third party auto dialers for advanced features like "reading a script".

Another new feature of the CHICA system will be automated physician order generation for HbA1C and FPG tests. When the CHICA system determines that a patient meets the criteria for type 2 Diabetes it will generate a just-in-time document using MLMs that contains the order. This just-in-time can be printed on paper to be handed to the patient, faxed to a predetermined lab, or called in using telephony interface.

While the CHICA system currently includes fax capabilities, which allows for faxed information to be deposited directly into CHICA and the medical record, we will be expanding these capabilities through the addition of automated faxed referrals from the CHICA system to pediatric endocrinologists. We will also program CHICA to receive, interpret, and deposit data from the pediatric endocrinologist regarding management plans into the CHICA database through a faxed structured letter.

C.3.1.2 Validation of the CHICA Type 2 Diabetes Module and Process to Address Technical Issues

We began building the CHICA system in 2002, and it has been in active operation since 2004. Therefore, we have a great deal of previous experience validating rule sets and addressing technical issues pertaining to database design, queries, parsing, annotation, context analysis, and missing data. We are aware of the many potential barriers/pitfalls that can be encountered during this process and we therefore have developed a process to overcome these potential issues and to maximize the benefit of the technology.

All rules and rule sets developed for use with the CHICA system undergo thorough testing prior to implementation within the "live" CHICA system. We begin by reviewing the logic behind all rules and rule sets in the CHICA User's Group (CHUG)meeting, an expert panel consisting of both health care providers and CHICA programmers to make sure that they appear valid. We then proceed to simulations, running the rules with test patients to make sure that they are triggered accurately. After rule deployment, we meet monthly with the CHUG, and review all CHICA process data in weekly team meetings to make sure that randomization and rule firing appears valid. Should any issues arise, we will strive to implement fixes in a timely manner.

We have (and will continue to have) one programmer who is always on call to perform technical support, in addition to this, a less technical member of the CHICA team will rotate full time through the clinics to assess CHICA's use and note any issues or problems for the full team to address. Further, the CHICA team leader and one of the programmers meets with physicians and staff on a regular schedule at the clinics over breakfast or lunch to allow clinic personnel to address members of the CHICA team directly.

C.3.2 Demonstrate both the feasibility and effectiveness of the CHICA Type 2 Diabetes Module to recognize those children in need of screening for Type 2 diabetes and facilitate diagnosis and clinical management of the condition (Aim 2)

Phase two of this proposed project consists of the randomized controlled trial of the CHICA Type 2 Diabetes Module (built in Phase one), evaluating primarily process measures. Work on this phase of the project will begin in quarter 1 of year 2 and will continue through quarter 2 of year 4.

C.3.2.1 Randomization

Presently, the CHICA system is utilized in four primary care practices affiliated with the Indiana University Medical Group-Primary Care (IUMG-PC) practice network. In 2009, these four clinics (Wishard Pediatric Primary Care, Pecar Health Center, Blackburn Health Center, and Forest Manor Health Clinic) hosted around 7000 patient visits for children ages 10 and older, the target population for this study. However, children within the age range with a pre-existing (pre-intervention) diagnosis will be excluded from the study. This corresponds to over 3,800 unique patients. Therefore over a 24 month timeframe we can conservatively anticipate that at least 4000 unique patients ages 10 and older will be seen in these four clinic sites. Additionally, these four clinic sites serve a large minority population, who are at greatest risk for developing type 2 diabetes (44% Black, 21% Hispanic).

The randomized controlled study will be conducted in these four clinic sites; two of the clinics will function as an intervention group and two will function as the control group. The unit of randomization will be the primary care clinic, but the unit of analysis will be the individual patient. Allocation of clinics to intervention or control groups will involve a randomization scheme in which the clinics will be ranked by the number of physicians staffing the clinic. One of the two largest clinics will be randomized to the intervention and the other to the control condition, and subsequent clinics will be alternately assigned to intervention and control such that each clinic can be matched to its most similarly sized clinic.

We chose a cluster randomization by clinic because contamination is a major concern. If we randomize at the physician level, physicians in the same clinic who are assigned to different treatment arms might communicate regarding the CHICA Type 2 Diabetes Module in terms of its operation and consequences, which would contaminate the control arm. Similarly, if we randomize at the patient level, physicians will tend to carry intervention methods to control patients, copying and utilizing intervention materials. Indeed, this has been our experience with other studies of the CHICA system.[29,30,33] Moreover, the on and off usage of the CHICA Type 2 Diabetes materials such as the physician worksheet and just-in-time handouts leads users to think that CHICA is malfunctioning.

Although this cluster randomization scheme imposes a number of challenging issues in terms of study design and data analysis, it is the optimal approach due to the reasons stated above. The limitation of randomization at the clinic level is cluster effects requiring larger sample sizes and potential bias caused by unknown characteristics related to the outcome that are differentially distributed in the four clinics. We have taken the clustering effect of the cluster randomization scheme into consideration for the determination of the sample size and the analysis plan (See sections C.3.2.8 and C.3.2.9).

C.3.2.2 Intervention Group

The two intervention clinic sites will have the CHICA system AND be provided access to the newly developed CHICA Type 2 Diabetes Module, the flow of which is depicted in Figures 1 and 2 and previously described in section *C.3.1.1*.

C.3.2.3 Control Group

The two control clinics will have the CHICA system but will *NOT* have access to the CHICA Type 2 Diabetes Module. The CHICA system will notify the physician of the child's BMI percentile on the physician worksheet. However, the CHICA system will not ask for any additional information related to risk factors for type 2 diabetes on the pre-screening form, no advice will be provided to the physician on the physician worksheet, nor will just-in-time documents or automated reminder calls be made available. Identification of patients at risk for type 2 diabetes and care of those patients will occur through routine practices for that clinic.

C.3.2.4 Recruitment

We will ask for a waiver of consent for this portion of the study as 1) there is little risk involved in supplying physicians with guidelines of care, 2) study procedures are within standards of usual care, 3) informing families that they may be part of a type 2 diabetes study could bias their response to screening questions and invalidate any and all results of the project, and 4) obtaining informed consent from the many thousands of patients who are seen at IUMG-PC clinics would be difficult and would itself create, because of the paperwork that would be required, a much higher risk of loss of patient confidentiality.

C.3.2.5 Measures

For Aim 2 of this project the primary outcome measure of interest is the percent of children ages 10 and older with documented risk factors for type 2 diabetes. The table below shows both our primary outcome measure along with secondary process and outcome measures of interest**.**

Measure
Primary Outcome Measure
Percent of children (ages 10 and older) with documented risk factors for type 2 diabetes (>85%BMI and 2 of 4 Risk Factors)
Diagnosis Related Process Measures
For those children (ages 10 and older) with documented risk factors for type 2 diabetes: • **Percent scheduled for FPG** • **Percent completing FPG** • **Percent scheduled for follow-up appointment with pediatrician** • **Percent attending follow-up appointment with pediatrician** **For those children (ages 10 and older) with "Borderline" FPG or HbA1C Labs:** • **Percent scheduled for OGTT** • **Percent completing OGTT** • **Percent scheduled for follow-up appointment with pediatrician** • **Percent attending follow-up appointment with pediatrician**
Diagnosis Related Outcome Measures
For those children (ages 10 and older) with documented risk factors for type 2 diabetes: • **Percent with "Positive" FPG Lab results (FPG > 125)** • **Percent with "Borderline" FPG Lab results (125 ≥ FPG > 100)** • **Percent with "Positive" HbA1C (HbA1C ≥ 6.5%)** • **Percent with "Borderline" HbA1C (6.5% > HbA1C ≥ 5.7%)** **For those children (ages 10 and older) with "Borderline" FPG or HbA1C Labs:** • **Percent with "Positive" OGTT (OGTT > 199)**
Referral Related Process Measures
For those children (ages 10 and older) with "Positive" FPG or HbA1C Lab results (FPG > 125) or HbA1C ≥ 6.5%): • **Percent referred to pediatric endocrinologist** • **Percent attending appointment with pediatric endocrinologist** • **Percent with follow-up letter sent to pediatrician by pediatric endocrinologist** **For those children (ages 10 and older) with OGTT > 199:** • **Percent referred to pediatric endocrinologist** • **Percent attending appointment with pediatric endocrinologist** • **Percent with follow-up letter sent to pediatrician by pediatric endocrinologist** **For those children (ages 10 and older) with OGTT between 140 and 199):** • **Percent referred to pediatric endocrinologist** • **Percent attending appointment with pediatric endocrinologist** **Percent with follow-up letter sent to pediatrician by pediatric endocrinologist**

C.3.2.6 Data Collection Procedures
In order to evaluate the process measures identified above, data will be collected via medical record abstraction and through review of CHICA data for both the intervention and control clinics. As the primary process measure of interest for this Aim is the percent of children ages 10 and older with documented risk factors for type 2 diabetes, a patient's chart will be eligible for chart abstraction if the child is age 10 or older. We will select a random sample of 250-350of these charts per clinic for a total of up to 750 per study arm (See Section C.3.2.7 for Sample Size calculation).

Research assistants (RAs) will be trained to review both the electronic medical record and paper charts for a variety of information related to screening and diagnosis of type 2 diabetes. To prepare for chart abstractions, we will secure copies of paper charts and access electronic charts, including charts of children identified with a type 2 diagnosis in CHICA or RegenstriefMedical Record System.To assess the reliability of chart abstraction, a random sample of 20% of the charts will be abstracted twice.

Eligibility and Consent for Physician Population:
All physicians (including residents) practicing in the targeted clinic sites (approximately 50) who utilize the CHICA system will be eligible to participate in this study by default. We will obtain informed verbal consent because data will be collected from surveys of physicians (non-patient adults) without identifying information. The survey, which will be hand-delivered to physicians by PResNet staff, includes 5 questions, and require approximately 5-10 minutes to complete. The survey will incorporate Likert scales to measure physician's use of the ADA guidelines for screening, diagnosing, and treating childhood type II diabetes. PResNet staff will be responsible for data entry and reporting of these data to study investigators.

C.3.2.7 Sample Size and Power Estimation
We determined the sample size to ensure adequate power to test the efficacy of the CHICA Type 2 Diabetes Module, as proposed in Specific Aim 2. The primary outcome is type 2 diabetes screening, measured at the subject level. The current screening rate for type 2 diabetes is known to be low. We estimate the screening rate to be approximately 10% in our clinics.

In a study of a predominantly low-income, Mexican American population, Drobac and colleagues reported that 20% of the children aged 10 to 18 years had a BMI above 85 percentile and at least 2 additional risk factors for type 2 diabetes, including family history of type 2 diabetes, high-risk race/ethnicity, and evidence of insulin resistance.[8] Kong and colleagues considered a BMI above 85th percentile as a fourth risk factor and reported that 60% of the children had two or more risk factors while 27% had three or more risk factors.[35] We expect that more than 20% of the children ages 10 and older will have a BMI above the 85th percentile and at least two of the four risk factors and hence will be screened in the intervention group.

If randomization were performed at the subject level, using a chi-square test and setting the alpha level at 0.05, we would have 80% power of detecting a 10% difference in the proportion of children screened for type 2 diabetes between the intervention and control groups with a total effective sample size of 438 patients.

Since the randomization is at clinic level, responses from subjects within the same clinic are likely correlated, causing a decrease in analytical power. The magnitude of power reduction depends on the level of heterogeneity of the clinical sites; such heterogeneity is often characterized by the intra-clinic correlation. Although we do not anticipate much variability in the four participating clinics, we will assume that the screening rate using standard care is 9% and 11% for two clinics and 10% for the remaining two clinics. Conservatively, we have estimated that the numbers of children age 10 or older seen in the four clinics are approximately 400, 500, 800, and 1500. This gives an intra-clinic correlation of no more than 0.006. Using this conservative estimate of intra-clinic correlation, we need to enroll 317 children per clinic. Note that this is a conservative sample size also because our pseudo randomization scheme is a matched-pair design, which has been shown to provide an improved power than the unmatched studies.[36] Based on our past experience, we do not anticipate dropout to be more than 10%. To compensate for the potential sample attrition, we will inflate the estimated sample size to 250-350 per clinic.

C.3.2.8 Data Analysis

Since our proposed study is a cluster randomized trial, the analysis plan should take the clustering effect into consideration. Commonly used approaches include aggregated cluster-level data analysis, random effects modeling, or generalized estimating equations (GEE) approach.[37] The cluster-level approach has the drawback of not being to fully account for individual-level variables that may be imbalanced across clusters, while the GEE approach requires a large number of clusters in the study. We therefore choose to use the random effects model. In Aim 2, the primary outcome is whether a child is screened for type 2 diabetes. This dichotomous variable will be modeled using the logistic regression analysis with random clinic effects to accommodate the potential dependence of responses from subjects within the same clinic. The fixed covariates will include treatment group, as well as potential confounders, such as age, gender, race, and other clinic and subject level characteristics. Potential interaction effects among covariates, especially interactions between treatment group and subject and clinic characteristics, will be examined to determine the effect of the intervention in different subgroups. The model will be fit using the SAS procedure NLMIXED. It should be noted that incorporation of relevant subject and clinic characteristics in the regression model usually reduce the clustering effect and thus increase the actual analytical power.[38]

Secondary outcomes, for example, whether a child was scheduled for a lab test, will also be analyzed using similar models.

C.3.2.9 Missing Data Analysis

Past experience shows that the CHICA system had a high data completion rate, with only 1.3% error rate due to omission of a data field. Such a low rate of missing data is likely to have a negligible impact on the analysis. However, for the longitudinal outcomes in Aim 3, we anticipate a higher rate of missing data due to the 10% dropout rate. If the dropout of subjects can be considered as Missing at Random (MAR), the random effects model would provide unbiased inference.[39] Multiple imputations will be performed under circumstances where compromise of power due to missing values is of concern. A regression approach that takes into account the baseline characteristics and baseline outcome measures will be used to impute the missing outcome. The SAS procedure MI and MIANALYZE will be used to implement the procedure. We also plan to perform a comprehensive sensitivity analysis assuming different missing mechanisms. In addition, a pattern mixture analysis will be conducted, where subjects are divided into groups depending on their missing data patterns and variables based on these groups are included in the mixed effects model.