SEARCH MOP - Section 12
Registry and Cohort Visits
Physical Measures, Laboratory Measures (Specimen Collection Form), Data Collection Forms

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12. Registry and Cohort Visits

12.1. OVERVIEW

When conducting Registry and/or Cohort visits, study coordinators will use good clinical standard practice.

12.1.1. *Registry Visit Overview (refer to Appendix A for further lab explanation)*

The Registry Visit will be completed for eligible cases diagnosed in 2012. Those with a Secondary form of diabetes are not eligible for a visit. The following 2012 incident cases will be eligible for a Registry visit: all minority cases, all cases age 10 and over at diagnosis, all non-Type 1 diabetes, and a 50% sample of the non-Hispanic white (NHW) cases with Type 1 diabetes diagnosed under age 10. In summary, the goal is to invite all eligible 2012 participants EXCEPT those that are known to be NHW, less than 10 years old, have Type 1 diabetes AND are born on an even numbered day of the month. (02/12) See Table 12.1 for specific data collection to be done at the Registry Visit.

Table 12-1 Registry Visit Data Collection

Eligible	Registry Visit Data Collection
Complete visits on the following 2012 cases: ▪ All minority cases (regardless of age or type) ▪ All cases age 10 and over at diagnosis (regardless of type or race/ethnicity) ▪ All non-type 1 cases ▪ Type 1, Non-Hispanic white cases under age 10 at diagnosis AND are born on an odd numbered day of the month	*Initial Participant Survey* (if not completed prior to study visit) *Physical Exam* Height/Weight, waist circumference, BP, acanthosis nigricans *Medication Inventory* List of currently prescribed medications *Lab/specimens* Blood, 1st-morning urine, and spot urine. Diabetes autoantibodies (GAD65, IA2, ZnT8), HbA_{1c}, fasting glucose, C-peptide, lipids, creatinine, and urinary albumin/creatinine *Participating Relatives* Any relatives participating in SEARCH *Contact Information* Current contact information for participant *Storage* Serum, plasma, DNA and DNA repository, and urine

Recruitment Criteria for the SEARCH Registry Study Visit

The following is the decision rule for determining whether to invite a potential participant to attend a SEARCH 3 Registry visit.

Is the child known to be non-Hispanic White (NHW)?

If NO: *Invite the child to attend a Registry Visit*

If YES:

Was the child under 10 years of age at diagnosis?

If NO: *Invite the child to attend a Registry Visit*

If YES:

Is the child known to have Type 1 diabetes?

If NO: *Invite the child to attend a Registry Visit*

If YES:

Can you determine the day of the month that the child was born?

If NO: *Invite the child to attend a Registry Visit*

If YES:

Is the child born on a day of the month that is an odd number (1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, or 31)?

If YES: *Invite the child to attend a Registry Visit*

If NO: Do not invite the child to attend a Registry Visit. Record in the tracking database and on the web report that this child was NOT invited to attend a Registry Visit.

If at any point in this decision process you are unsure of the answer to any of these questions (age at diagnosis, type, birthday, etc.), then you can invite the child for a Registry Visit.

In summary, the goal is to invite all eligible participants EXCEPT those that are known to be NHW, less than 10 years old, have Type 1 diabetes AND are born on an odd numbered day of the month. (2/12)

<u>When scheduling participants please note the following</u>:

- Fasting visits are strongly preferred.
- Participants that are pregnant cannot take part in a study visit until 4 months after the end of the pregnancy. When appropriate, ask the participant if she is pregnant prior to scheduling the visit.

- All components of the Registry study visit should ideally be completed on the same day. If that doesn't happen, complete all elements within three months.

Case Ascertainment Windows:

Based on the 30 month window, the following current dates for in window ascertainment are:

Incident year	Close of window	
2010	June 30, 2013	
2011	June 30, 2014	
2012	June 30, 2015	(Note: grant ends 9/30/15)
2013	June 30, 2016	(If 1 year extension is granted, 2013 cases can also be included)
2014	June 30, 2017	
2015	June 30, 2018	

Based on the decision above, cases may continue to be registered up until 9/30/15 (end of grant) or 9/30/16 (pending approval of a 1-year extension). NO LATE CASE REGISTRATION WILL OCCUR AFTER THE CLOSE OF EACH YEAR'S WINDOW

What is closing date for entry of core data?

As above, ALL RELEVANT DATA FORMS (IPS, extended core form) may be entered up until the close of the window for each year. At a minimum, this includes date of birth, date of diagnosis, sex, race/ethnicity and diabetes type.

What is closing date for any 2012 in-person registry visits?

Close of the 2012 window is June 30, 2015. VISITS SHOULD BE COMPLETED AND ENTERED NO LATER THAN THIS DATE.

What should be done during the 2014-2015 incidence years?

Data should be collected and entered until 9/30/15 (end of grant) or until 9/30/16 if extended. (8/12)

12.1.2. *Cohort Visit Overview (refer to Appendix B for further lab explanation)*

The Cohort visit will be completed for eligible incident cases diagnosed in 2002-2005, 2006, and 2008. To be eligible for a Cohort Visit the participant must have completed at least a baseline visit, had diabetes for a minimum of five years, and not had a SEARCH visit within two years. A Cohort Study Eligibility report has been developed by the Coordinating Center and is available on the website. When assigning earliest recommended visit dates, consideration was given to visit intervals such that for 2002 -

2006 cases the recommended date for the opening of the cohort visit window was set to the later of EITHER the baseline visit plus five years OR the last in person visit plus two years. However, for 2008 incident cases additional consideration was given to the overall timeframe of SEARCH 3 and the criteria for the earliest recommended visit date is the later of the diagnosis date plus 5 years or the last SEARCH visit plus 2 years (see section 1). Sites should mark a case as Do Not Contact or Refusal on the website in any of the following instances: participant is deceased; participant completed a baseline visit in error (was never eligible for a visit); or the participant has refused any further contact with SEARCH. Participants marked as such will be removed from the Cohort Eligibility Report and the total number of eligible participants. An individual may be scheduled for a Cohort Visit starting up to 1 month prior to when their visit window opens, and anytime thereafter.

When scheduling participants please note the following:

- Fasting visits (at least 8 hours fasting overnight) are strongly preferred.
- Participants who are pregnant cannot take part in a study visit until 4 months after the end of the pregnancy. When appropriate, ask the participant if she is pregnant prior to scheduling the visit. Otherwise, the question will be asked at the time of the visit.
- If a participant refuses an in-person Cohort Visit (or is unable to take part due to geographic or other logistical barriers), sites should attempt to complete forms through the mail (for self-administered forms) and on the telephone (interview for Family History form).
- If a participant is a 'just not right now' participant, they will remain in the group of people "pending" a visit. Sites should track "pending" a visit locally (i.e., perhaps the participant indicates to call back in the summer, for example.) Sites would only move the participant into the 'refusal' category once all options for the visit have been exhausted and the site has assessed they have refused the visit.
- There will be three categories for participant refusals:
    - 1. **Do not contact** - being someone who refuses this visit and all other contact - remove from denominator
    - 2. **Refusal** - being someone who refuses this visit only (either actively or passively) but might be interested in future efforts - remains in denominator
    - 3. **Unable to contact** - being someone for whom we have inadequate contact info and can't get to/find them to find out if they will do the visit - remains in denominator.

- Because we are unsure how food intake may affect the SphygmoCor testing, it is our goal to minimize the effects of food. In order to apply uniformity between sites and from one participant to another, we all participants should be given a standard snack (Nutri-Grain bar) after the collection of the fasting blood samples. Participants should take insulin with this snack according to their usual regimen. After the snack has been consumed, study staff will measure the participant's blood pressure (per SEARCH protocol). Immediately following the blood pressure measurements, SphygmoCor testing will begin. The outline below suggests the preferred order of procedures. To allow sites flexibility to address unique issues related to the implementation of the cohort visit, some of the measures can be performed in any order and it is permissible to collect the data at 2 separate visits. If the data collection visits are split, the time period between them should be minimized as much as possible and should not exceed 3 months.

Table 12-2: Cohort Visit Data Collection

Eligible	Cohort Visit Data Collection
Eligible cases must meet the following criteria: ▪ Diagnosed in 2002-2005, 2006, 2008 ▪ Previously completed a visit in SEARCH ▪ Minimum of five years since diabetes diagnosis ▪ Not had a SEARCH visit within the previous two years **Note**: **Sites will base the order of recruitment and scheduling on eligibility lists developed by the Coordinating Center**	**Lab/specimens**: Blood ▪ Fasting glucose ▪ DAA (GAD65, IA2, ZnT8 [once assay is standardized]) ▪ Fasting C-peptide ▪ Fasting lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) ▪ A1c ▪ ApoB ▪ LDL particle size and density ▪ Cystatin-C ▪ CRP ▪ IL-6 ▪ Fibrinogen ▪ Adiponectin ▪ Leptin ▪ Creatinine ▪ storage of plasma, serum, DNA, and DNA repository Urine (see table 12-3 for more details) ▪ urinary albumin and creatinine (including first morning void and random sample) ▪ storage of urine
	Physical Exam height, weight, waist circumference, BP, acanthosis nigricans
	Michigan Neuropathy Screening Instrument (MNSI) Foot exam and questionnaire
	Questionnaires
	Retinal Photos Retinopathy and retinal vessel caliber
	Cardiac Measures (SphygmoCor) Heart Rate Variability (HRV), Pulse Wave Velocity (PWV), Pulse Wave Analysis (PWA)

12.2. PROCEDURES COMMON IN REGISTRY AND COHORT VISITS

12.2.1. *General Information*

Missing Data Collection

There will be instances when one or more components of the in-person visit are not completed. This may occur for a variety of reasons, such as participant or parent refusal, inability of participant to complete interviews or questionnaires due to developmental delay, or lack of participant cooperation. If one or more components of the in-person visit are not completed, a brief explanation should be written on the corresponding forms. When these un-used forms are entered on the data entry section of the website, check the box under "Form Disposition", and enter the information in the grey "For Study Use Only" section at the end of the form. When a participant refuses or is unable to respond to an individual question within an interview or a questionnaire, the response should be recorded and data-entered as "-9" (or "1800" for unknown dates).

Data Entry of Consent Forms

A web-based form will be data-entered for every Phase 3 consent form that is signed. A consent tracking form has been provided (on the website), but not required that can be placed in the visit packets (that is, the packet of all the various forms needed for the visit) for cohort and registry visits. The coordinator who completes the visit would also complete the form at the time of the visit. It would be included in the packet to be data entered. In some rare instances, information may change on a participant's hardcopy Phase 3 consent form. A corresponding change may be needed on the data-entered version to keep the two consistent with one another. Refer to section 6.3.3 for details.

Procedures for Participants Transferring to another SEARCH Site

Participants transferring to another SEARCH site remain registered at their original site of registration; therefore, the participant's PID remains the same. Participants are not to be un-registered because they are moving or have moved. If the "new" site inadvertently re-registers the participant, the 'new' site must un-register the participant using "other" as the reason.

If a SEARCH Study participant meets the eligibility criteria as an incident case at one SEARCH center, and then moves to another eligible SEARCH center within his/her incident year, then the site where the participant lived closest to the date of diagnosis is the site that should register this participant.

For participants who transfer, visit scheduling and follow-up will be done at the new site. The old site will notify the new site when a participant is eligible for a visit so they can attempt to schedule a study visit.

Whenever data are collected at the new site, the forms will be mailed (preferably FedEx'd) to the old site to be data entered. The new site should retain copies of all forms mailed to the old site. The old site will receive any data validation queries at the time of data entry.

Both sites should be looking at medical records since they may exist at either site. Extended Core and Medical Record Validation worksheet information (if applicable) should be sent to the old site to be data entered.

Lab results will be sent from the lab to the old site. The laboratory will notify the old site of participants who need repeat urine samples. Notification of alert values or scores will be sent to the old site.

Participants should be (re)consented at the site where they complete the visit. Copies of these consents should be sent to the original site for storage in the participants' files. (08/13)

12.2.2. *Physical Examination*

Note: Physical examinations are only to be conducted on eligible participants **3 years of age or older**.

Scientific Rationale

Height and weight are the mainstays of anthropometric measures in epidemiological studies and have been used to assess the degree of an individual's obesity or thinness [1,2]. Waist circumference, an index of deep adipose tissue and general obesity has also been found to correlate with fat mass. Since obesity is a known risk factor for the development of type 2 diabetes in adolescents; height, weight, and waist circumference will be recorded for all participants who are three years of age or older. Body mass index will be calculated to assess each participant's obesity or thinness [3,4]. These measures will be used to assess the frequency of obesity or thinness in each type of diabetes. These and other clinical measures will then be used to develop a clinical profile for each type of diabetes that may help clinicians identify the likelihood that a participant has a specific type of diabetes based on clinical criteria.

Equipment and Supplies

- **General**: Screened area for privacy with secure place for storing participant valuables with measurements made in a warm, well lighted room
- **Height**: portable stadiometer, wooden block, centimeter measuring stick
- **Weight**: portable electronic scale, weighs in kilograms with graduations of at least 0.1 kg., capacity of at least 200 kg

- **Waist Circumference**: non-tension, tape measure with a leading blank zero segment, which measures in centimeters with graduations of at least 0.1 cm, length of at least 150 cm.
- **Blood Pressure**:
  - **Manometer**: Welch Allyn Tycos 767-Series Mobile Aneroid manometer (Modification for a stand to allow table top use is permitted).
  - **Blood pressure cuffs**: 5 sizes: infant, child/adult, adult, large adult, and thigh.
  - **Stethoscope:** stethoscope with adult and pediatric double heads, including diaphragm and/or bell.

Height

Calibration of Equipment

Portable stadiometers will be calibrated annually or according to manufacturer's guidelines. Equipment must meet the following standards for use in this study:

- Stadiometer: adjusted to within 0.1 cm of the measuring rod

Measurement Approach

Height is measured and recorded twice. A third measurement is made only if the second measure differs from the first by ***> 0.5 cm.***

Outer clothing and shoes will be removed. The presence of a non-removable appliance (e.g., cast or brace) will be noted.

Height is measured in centimeters, using a stadiometer. The participant will stand erect with the heels, buttocks, and shoulders tangentially against the measuring device (see Figure 1). The heels will be together with the feet at a 45-degree angle to each other in a comfortable stance. The participant will look straight ahead. The participant will then be told to take and hold a deep breath making himself/herself as tall as possible.

Figure 1.

It is preferable to have participants with tall hairstyles take down their hair so the bar on the Stadiometer (specifically the portable Road Rod™) can be used as designed (sliding perpendicular measurement guide onto the top of the head).

The Road Rod™ height measurement bar is designed in a way that takes the actual measurement using a pointer that extends above the level of the head by slightly more than an inch. The placement of the pointer on the measurement device is corrected (by design of the Road Rod™) to result in the correct height.

The observer makes sure that the heels are on the floor and in the correct position. The sliding head projection bar is then brought firmly down on the crown of the head and secured; and the stature is recorded to the nearest tenth of a centimeter (see Figure 2).

Figure 2

Large participants may find it uncomfortable to stand with their feet too close together. To prevent sway, these participants will be instructed to stand with their feet as close together as possible while maintaining a comfortable stance. A wooden block is used to align the feet of larger participants should the size of the buttocks prevent the heels from aligning tangentially against the measuring device.

Documentation

The following is an example of height documentation:

1. Height:

1	2	0	.	2	cm.	1	2	0	.	4	cm.				.		cm.
First						Second						*Third					

*Third measurement required if first two measurements differ by >0.5 cm.

1a. Was a knitting needle used with the Road Rod?

1 ☒ Yes

2 ☐ No

Weight

Calibration of Equipment:

Scales will be calibrated annually or according to manufacturer's guidelines. Equipment must meet the following standards for use in this study:

- Scales: calibrated to within the nearest 0.2 kg using standard weights

Measurement Approach

Weight is measured and recorded twice. A third measurement is made only if the second measure differs from the first by > ***0.3 kg.***

Participants should be encouraged to wear lightweight clothing preferably a top/shirt and bottom/pants, shorts. Outer clothing and shoes will be removed. Participants will be encouraged to empty their bladder and bowels prior to any measurements (the urine can be used for the spot urine). The presence of a non-removable appliance (e.g. cast or brace) will be noted.

Body weight is measured in kilograms, using an electronic scale. There are two approved weight scales: SECA model 770 and model 876.

Figure 3
Model 770 Model 876

Note: Manufacturing of model 770 has been discontinued. However, sites that still have model 770 scales that are operational may continue to use them. When replacement of the scale is necessary, sites will purchase SECA model 876.

- The scale is placed on a flat level uncarpeted surface.
- Confirm that the scale is balanced (zeroed). Balance if necessary.
- The participant will stand comfortably, arms at the side and looking straight ahead.
- The participant's feet will be parallel, but not touching, and centered on the scale platform; and the weight is recorded to the nearest tenth of a kilogram. Address the common error 16 that appears on the scale and indicate that the scale needs to be tapped in order to make the scale balance out. If it is only the one scale that has this problem, it may not need to be addressed.

Note: The SECA 876 scale measures to the 0.1kg for weights ≤150kg and to 0.2kg for weights >150kg. The SECA 770 measures all weight ranges to the 0.1kg.

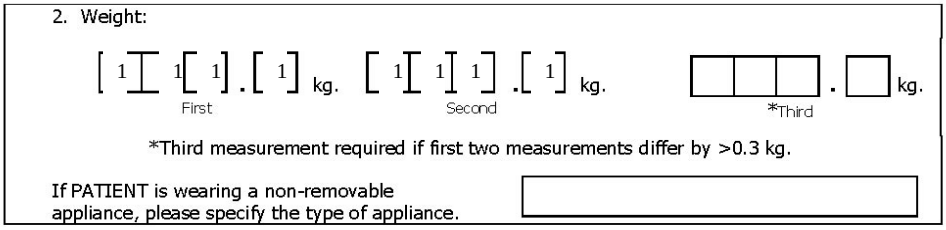
Some scales may be capable of measuring to the nearest 0.05 kg. If weight measurements are taken with scales measuring to the nearest 0.05 kg, **ignore the last digit and record the weight to the nearest tenth.**

Document **both** weight measurements. A third measurement should be taken if the first two measurements vary by > 0.3 kg. **Note: Scales used for weight measurement must have the capability of weighing to the nearest 0.1 kg for weights ≤150kg and at least to the 0.2kg for weights >150kg.**

The SECA model 876 scale has an Adult-Child Function that allows a child to be weighed while being held by an adult. This feature should be used only when the child is unable to be weighed on the scale alone. If the Adult-Child Function is necessary, the adult is weighed alone first. Then the Adult-Child button is pressed and the adult is re-weighed holding the child. The scale ascertains the difference between the two measurements and this value is recorded as the weight of the child.

Documentation

The following is an example of weight documentation:



Waist Circumference

Waist circumference is measured using two protocols distinguished by different anatomical landmarks:

a. "NHANES" (National Health and Nutrition Examination Survey) using the iliac crest and mid-axillary line as identification markers and

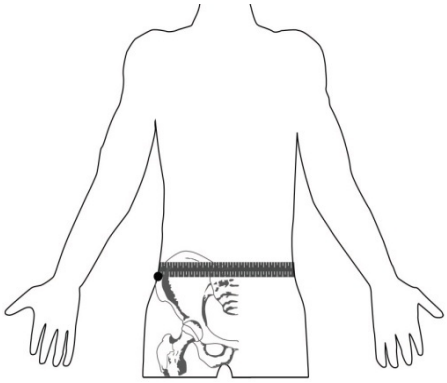
b. "Natural Waist."

Measurements are performed using a non-tension tape measure marked in centimeters that includes a leading blank segment. For participants whose waist circumference is equal to or less than 150 cm the tape is fiberglass; for larger participants the tape is made of flexible steel.

> The fiberglass tape measure required for this protocol is model BMS-8 (Creative Health Products).
>
> The flexible steel tape measure required for this protocol is the Anthropometric tape from Rosscraft.

For both protocols, waist circumference is measured and recorded twice. A third measurement is made only if the second measure differs from the first by ***> 1.0 cm.*** The participant should stand erect with abdomen relaxed, arms at their side, and feet together. Measurements should not be made over clothing. For measurement purposes, shirts will be lifted and pants lowered in order to expose the waist. This should be done in a way that will not change the natural contour of the waist. It is suggested this measurement be performed using two persons but for some participants, a single person can perform the measurement using a mirror to assure the horizontal alignment of the tape is maintained. The measurement should be taken at the end of the normal expiration with the tape snug but not compressing the skin.

"NHANES" Protocol for Waist Circumference



- Measurer should first stand at participant's right side to palpate the hip area for right iliac crest.
- With a cosmetic pencil mark a horizontal line just above the uppermost lateral border of the ilium. Then cross the line to indicate the line that drops from the middle of the axilla.
- Place measuring tape around the subject in a horizontal plane (parallel to the floor) at the level of the crossed lines on the right iliac crest.
- If, after palpating the hip area, the measurer has difficulty locating the iliac crest, instruct the participant to place his/her hands on both of their hips with the fingers placed anterior, thumbs placed posterior, and palms inferior. Use this area as a landmark and try palpating again.

"Natural Waist" Protocol

- Measurer should face participant.
- Place the measuring tape around the subject in a horizontal plane (parallel to the floor) at the level of the natural waist (midway between the lowest rib margin and the iliac crest in the line that drops from the center of the axilla). If the rib margin cannot be identified, the natural waist can be identified as the point of "natural bend".

Helpful Hint: In some children, it may be difficult to identify the natural waist. If the rib margin cannot be identified, the natural waist can be identified as the point of natural bend. The natural bend can be determined by asking the participant to lean to the side without swaying forward or backward. The point of natural bend can be marked with a blue cosmetic pencil and the measurement made at that level once the participant has returned to the upright position. Be certain that horizontal alignment of the tape is maintained.

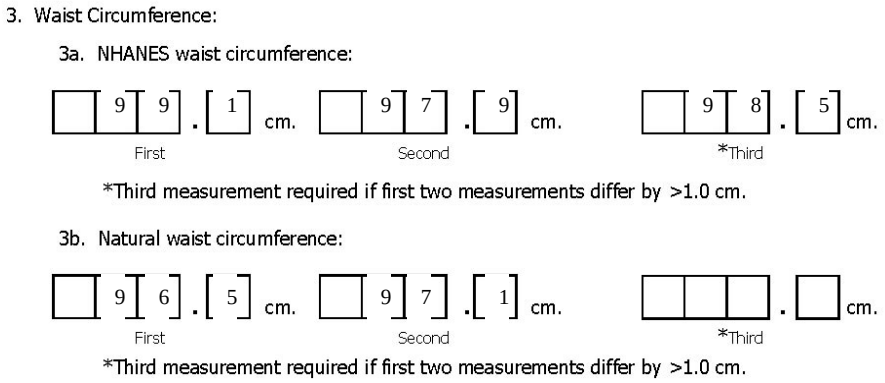
<u>Documentation</u>

Space is provided on the Physical Examination Form for each separate protocol of waist circumference. Caution should be used to be certain the appropriate measurements are placed in the appropriate section. The two protocols are likely to

yield different results, and either protocol might have a greater value. Note that neither protocol depends on the location of the umbilicus.

When measuring the waist circumference it is essential that the two protocols be measured separately, i.e., all "NHANES" measurements first, then all "natural waist" measurements.

Note: Within each protocol, a third measurement should be taken if the first two measurements vary by more than 1.0 cm.



Blood Pressure

Scientific Rationale

Risk of illness and death is related to changes in blood pressure. Hypertension is associated with cardiovascular disease and is a known complication of diabetes. Hypertension is also associated with the development of other types of complications, such as retinopathy and nephropathy [5]. Therefore, blood pressure will be recorded for all participants age three years or older.

Equipment and Supplies

- **General**: Screened area for privacy with secure place for storing participant valuables with measurements made in a quiet, warm, well-lit room
- **Manometer**: Welch Allyn Tycos 767-Series Mobile Aneroid manometer (Modification for a stand to allow table top use is permitted)
- **Blood pressure cuffs**: 5 sizes: infant, child/adult, adult, large adult, and thigh
- **Stethoscope:** stethoscope with adult and pediatric double heads, including diaphragm and/or bell.

Calibration of Equipment: The aneroid manometer is calibrated when it is manufactured. However, regular inspection of the blood pressure cuffs, tubing, stethoscope and manometer is necessary to eliminate conditions that could cause the

blood pressure to be measured as erroneously high or low. Additionally, a calibration check using the NeTech Digimano 1000 digital pressure-vacuum meter should be performed on the manometer at a minimum of every 6 months or whenever it is transported by car.

These checks should be performed on a daily basis:

a. Check for cracks on the manometer dial face
b. Check that the manometer needle is at 0mmHg when not under pressure
c. Check the cuffs, pressure bulb, manometer and stethoscope tubing for cracks or tears
d. Check the pressure control valve for sticks or leaks
e. Check stethoscope diaphragm for cracks
f. Equipment that is not working properly needs to be repaired or replaced. Never attempt to repair the equipment yourself.

The aneroid sphygmomanometer unit should be checked for accuracy every 6 months or when transported by car. Repair or replacement of the unit is required if the aneroid unit differs from the calibration device by 4 mm Hg or more.

Equipment required for accuracy check:

a. Pressure-vacuum meter (NeTech Digimano 1000)
b. Y-tubing and plastic adaptor (Y- or T-shaped)
c. Adaptor ends (female and male) for connecting Y-tubing to the aneroid unit and the blood pressure cuff tubing
d. Aneroid sphygmomanometer
e. Blood pressure cuff and bulb/valve assembly.

Aneroid Accuracy Check Protocol

(Adapted from the document "Protocol for Assessing the Accuracy of Aneroid Sphygmomanometers" by Carol Nash, RN, BSN and Vincent J. Canzanello, MD, Division of Hypertension and Internal Medicine, Mayo Clinic, Rochester, MN)

a. Disconnect blood pressure cuff from the sphygmomanometer.
b. Connect the long end of the Y-tubing to the coiled tubing of the aneroid unit using the female adaptor end.
c. Connect one short end of the Y-tubing to the Digimano pressure vacuum meter (does not require an adaptor end).

d. Connect the other short end of the Y-tubing to the blood pressure cuff tubing using the male adaptor.

e. Turn on the pressure-vacuum meter.

f. Select "mm Hg" as the type of unit to be measured.

g. Pump up blood pressure cuff until the aneroid unit reads 280 mm Hg. Check to see if the aneroid unit is within ±3 mm Hg of the readout on the pressure-vacuum meter. Record the pressure-vacuum reading on the calibration log under the "280 mm Hg" column.

h. Continue to deflate the cuff in 20 mm Hg increments along the entire range down to zero. Record the pressure-vacuum reading at each 20 mm Hg interval (280, 260, 240, etc.). Variations greater than ±3 mm Hg requires the unit to be removed from service and shipped to the manufacturer for repair or replacement.

i. After complete release of the pressure, make sure the aneroid unit "zeros". If complete "zeroing" does not occur, the aneroid unit should be removed from service and shipped to the manufacturer for repair or replacement.

Annual Certification of the Pressure-Vacuum Meter

The Digimano pressure-vacuum meter should be shipped to the manufacturer annually to be calibrated and certified. The process takes about 3-4 weeks and there is a charge for the service and shipping. A Certificate of Calibration will be returned with the meter.

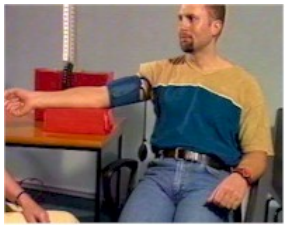
The Netech DigiMano digital pressure and vacuum meter is Part no. 200-2000IN. This meter can be purchased from the Netech Corporation for $345.00. (Vendor information - (Netech Corp. info. 1-800-547-6557 www.netechcorporation.com)

Measurement Approach

Before beginning blood pressure measurements, the participant should have been seated quietly for at least five minutes. The blood pressure should be measured following the collection of blood samples; and for the cohort visit, just prior to the SphygmoCor measurements. The right arm should be used for blood pressure measurements. If the participant or parent indicates any reason why these measurements should not be done with the right arm, the left arm may be used. If there is a problem with both arms, do not take the blood pressure.

In some sites it may not be feasible to collect blood pressure under these circumstances. This may be due to distance traveled, timing of visit, and anxiety about blood draw. Therefore blood pressure should be taken using the opposite arm in which blood was drawn.

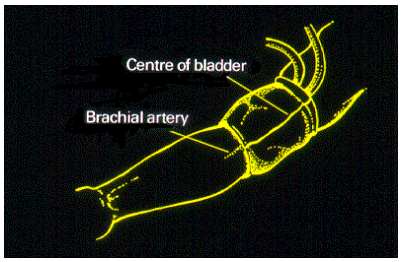
- In the SEARCH study, an aneroid manometer will be used to assess blood pressure.
- The manometer should be placed in a position that can be easily seen by the examiner and at his/her eye-level.



- The participant will be seated at a table in a relaxed, but not slouched, position with feet flat on the floor, if possible. For tall participants, it may be necessary to support the arm higher than a standard desk or tabletop.
- Place the tall participant's forearm on a pillow, large book or directory to raise the arm to heart level. For small participants, place a cushion or large book on the chair so the **arm is at heart level** when it is resting on the desk or tabletop.
- The right arm will be placed on the table, slightly flexed with palm upward. The arm should be positioned so that it is resting on the table at heart level (halfway between the shoulders and the waist). The elbow must not be lower than the lowest rib and must not be raised as high as the shoulder.
- Place a box or large book under the feet if they do not rest flat on the floor. If the participant is unable to sit, do not measure the blood pressure. The participant will be wearing clothing that is non-restrictive: short-sleeve or sleeveless top or gown. If they are wearing a top with sleeves, the sleeve should be rolled loosely up to the shoulder.
- The examiner will be seated facing and slightly to the participant's right, allowing easy access to the arm. After explaining the procedure to the participant, the examiner will locate the brachial and radial pulse points in the right arm.
- The right arm will always be used unless specific conditions prohibit its use. Use the following guidelines:

- If the radial pulse is apparent, whether or not the brachial pulse can be felt, proceed with the measurement of the first blood pressure.
- If the radial pulse cannot be felt in the right arm, use the left arm.
- If the radial pulse cannot be felt in either arm, the blood pressure should not be measured.

After locating the pulse points, select a cuff size that appears to be appropriate. Check the size before applying the cuff by making sure that the index line falls completely within the range lines. If the cuff is barely large enough, use the next larger size. If none of the cuffs (infant, child, small adult, adult, large adult, and thigh) are the appropriate size, do not measure the blood pressure. The procedure for applying the cuff is as follows:



a. Check the index line to determine if it lies completely within the range lines marked on the cuff.

b. Position the cuff at least 1” above the crease of the elbow. Place the artery arrow on the inner part of the cuff directly over the brachial artery.

c. Wrap the cuff smoothly and snugly around the arm. Cuff should be wrapped in a circular manner. No spiral direction of the cuff should be used.

d. Check the fit by placing both thumbs under the cuff and tugging gently. Should the cuff slip or come off, reposition and rewrap the cuff securely.

e. It is possible when using the larger cuffs that the cuff length from shoulder to elbow may be too long. If so, place the stethoscope bell head directly over the brachial pulse point under the cuff.

f. Cuff placement should not be altered once the Maximum Inflation Level (MIL) has been obtained. If the cuff needs to be refitted for any reason, the MIL must be measured again.

To determine the MIL, connect the inflation tubing to the manometer by twisting the two ends of the tubing together. The MIL is then determined as follows:

a. Locate the radial pulse point in the arm to be used.

b. Close the thumb valve. Feel the radial pulse and watch the needle of the aneroid manometer.

c. Inflate the cuff quickly to 60 mm Hg, then inflate in increments of 10 mm until the radial pulse disappears (or until 270 mm is reached), mentally noting the reading of the needle at that point. Continue inflating the cuff for another 30 mm at increments of 10 mm, pausing briefly to make sure the pulse is absent.

d. Rapidly deflate the cuff by opening the thumb valve completely and disconnecting the tubing.

e. Record the pressure required to obliterate pulse.

f. Add 30 mm to the reading at the point the radial pulse disappeared. Record this number as the MIL.

If unable to determine MIL, wait at least 30 seconds and make a second attempt. If still unable to determine the MIL, do not measure the blood pressure. If the radial pulse is still felt to a level of 270 mm Hg or higher (MIL 300 mm Hg), repeat the MIL and if it is 300 mm/ Hg, measure the blood pressure using 300 as the MIL. Record 300 as the systolic blood pressure and the measured 5th phase diastolic reading. Do not remove the cuff after measuring the MIL. If it is necessary to re-adjust the cuff after measuring the MIL, wait at least 30 seconds and repeat the MIL measurement.

Three consecutive blood pressure readings will be obtained using the same arm. Wait at least 30 seconds between readings. Open the thumb valve completely and disconnect the manometer tubing after each reading to reduce the pressure level to zero.

The following procedure will be used in measurement of the blood pressure:

a. Position the stethoscope comfortably in your ears with the earpieces turned forward, toward the nose.

b. Feel the brachial pulse and place the stethoscope diaphragm head directly over the pulse just below the cuff. The diaphragm should be applied with light pressure so that there is no air between the skin and the edge of the diaphragm. If the brachial pulse is too faint to be felt, place the stethoscope diaphragm over the innermost part of the elbow fold crease and proceed. If possible, avoid allowing the cuff, tubing, or stethoscope to touch. The following three situations would be indications for using the bell of the stethoscope: 1) when hard to hear, 2) with very small arms (i.e. babies and toddlers), 3) when the blood pressure cuff is riding low and would be pushing on the edge of the diaphragm.

c. Close the thumb valve. Rapidly and steadily inflate the cuff to the MIL. If you inflate the cuff more than 10 mm Hg above the MIL open the thumb valve, rapidly deflate the cuff and disconnect the tubing. Discontinue this reading and wait 30 seconds before inflating again.

d. When the MIL is reached, open the thumb valve and smoothly deflate the cuff at a constant rate of approximately 2 mm Hg per second (one mark per second).

e. Your eyes should be level with the center of the aneroid manometer dial. Watching the needle, note the reading at the point when pulse sounds first appear. Listen for at least two consecutive beats to eliminate recording a single erroneous sound. Note the reading at the point the first pulse sound appears, not at the second beat. This is the systolic blood pressure reading.

f. Continue deflation at 2 mm Hg per second. Note the reading when the sounds completely disappear. This is the fifth phase diastolic blood pressure reading.

g. Continue steady deflation at 2 mm Hg per second for at least 10 mm Hg below the diastolic reading; then open the thumb valve completely and disconnect the tubing. Let the cuff fully deflate. Wait 30 seconds between measurements.

h. Record the first reading (sounds appear) as the systolic pressure, the second reading (sounds disappear) as the diastolic pressure. Use the nearest even digit. If the needle fell between two digits, record the higher even digit.

i. In many instances in children, pulse sounds normally continue to be heard down to zero pressure. The diastolic reading should be recorded as “000”. Assure the participant’s parent, if present, that there is no problem.

j. Repeat this procedure for the second and third measurements and record measurements.

k. If unable to obtain 3 blood pressures, record reason on Physical Examination form.

If a measurement is unsatisfactory because of improper technique or instruction, that particular measurement can be repeated if you inflate the cuff on the participant’s arm no more than five times, i.e., two MIL attempts plus three blood pressure readings or one MIL and four blood pressure attempts.

If the blood pressure sounds are not heard during the first measurement, review your technique, check stethoscope position, check for loose connections or tubing kinks, and maintain a quiet environment. Relocate the brachial pulse and apply the bell head directly over the pulse point. Take care to wait at least 30 seconds between measurements. Use the following techniques to enhance the sounds:

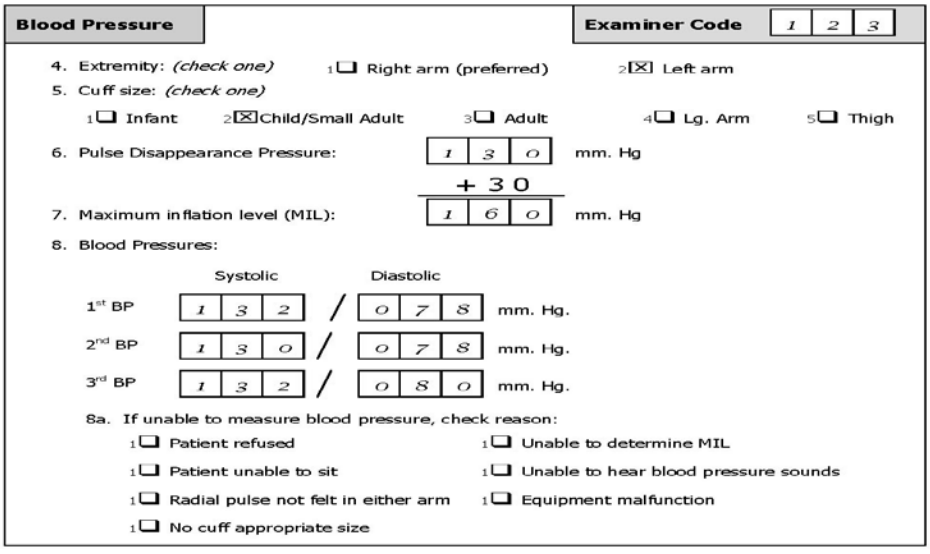
1. Have the participant raise his/her arm and forearm for at least 60 seconds. Then lower the arm, inflate the cuff, and measure blood pressure immediately; OR
2. Instruct the participant to open and close his/her fist 8 to 10 times. Inflate the cuff and measure blood pressure immediately.

If you still do not hear the blood pressure sounds during the second measurement, repeat above procedure until cuff has been inflated a total of five times.

Documentation

Documentation of the participant's blood pressure includes:

- The arm used to take the reading (right arm is preferred)
- The cuff size (e.g., child, adult, thigh)
- The pressure at which the pulse no longer becomes palpable
- The maximum inflation level (pulse pressure PLUS 30 mm/Hg), and
- **Three** blood pressure readings. *Note: Remember to wait for a minimum of 30 seconds between the first and second measurements and the second and third measurements.*



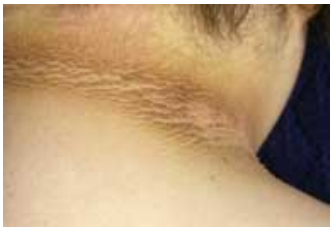
Alert Values

Individual participant blood pressures will be compared to a table of blood pressure levels at the 95th percentile (per the NHLBI guidelines table), based on the participant's gender, age, and height percentile. If the participant's blood pressure (systolic and/or diastolic) is greater than the 95th percentile, the participant or the parent/legal guardian <18 years of age will be informed that the participant's blood pressure is higher than expected. If the participant is not already being monitored and treated for high blood pressure, study personnel will recommend that they follow-up with their healthcare provider. However, if the BP is greater than the 99th percentile plus 5, the study staff will ask that the participant seek immediate medical attention within the next three days. Staff personnel should provide documentation to the participant the BP value collected and document the BP result and in the participant's research record noting the participant was informed to seek immediate medical attention. (See Appendix C for the 90%ile, 95%ile and 99%ile+5 Blood Pressures by Gender Age Height). (6/12)

Acanthosis Nigricans

Scientific Rationale

Acanthosis nigricans is an eruption of the skin characterized by hyperpigmentation and velvety cutaneous thickening that can occur on any part of the body but characteristically affects the axillae, the posterior portion of the neck, the groin, the antecubital and popliteal surfaces and the umbilicus. Acanthosis nigricans is now recognized as a sign of insulin resistance [6]. Insulin resistance, however, can occur in the absence of acanthosis nigricans [7]. A higher prevalence of acanthosis nigricans is found in ethnic populations with darker skin than lighter skin [6]. Studies in children and adolescents demonstrated that the neck was most significantly affected and always involved when other areas of the body have acanthosis nigricans [8]. In a field study of children, the anatomical area that proved to be the most reproducible was the neck [9]. Changes in texture must be present to identify acanthosis nigricans [8].



Acanthosis nigricans of neck

Equipment and Supplies

None

Measurement Approach

Acanthosis nigricans will be assessed for all participants by comparing the texture of the forearm with palm facing up and the texture of the nape of the neck. The participant will face the examiner with hands at their side and hands in the supine position. The examiner will face the participant and slowly and gently run their finger down the anterior aspect of the mid-portion of the forearm mid-way between the antecubital fossa and the wrist to assess normal texture (smooth). The participant will then turn around with their back to the examiner. The examiner will inspect the posterior portion of the neck from pinna of the right ear to pinna of the left ear. The examiner will divide this area into four quadrants and slowly and gently run their fingers from superior to inferior in each of the quadrants. The presence of "rough" texture in any quadrant will identify the presence of acanthosis nigricans. The presence of increased pigmentation only does not denote acanthosis nigricans. The presence of acanthosis nigricans will be recorded as **YES, NO, or MAYBE**.

Documentation

The following is an example of Acanthosis Nigricans documentation:

Acanthosis Nigricans		Examiner Code			
9. Is Acanthosis Nigricans: *(check one)*	1❑ Yes	2❑ No	3❑ Maybe		

12.2.3. *Laboratory Measurements*

Overview

This section provides a brief overview of the laboratory procedures to be collected on SEARCH participants. Further information regarding obtaining, handling, and shipping specimens to the SEARCH Central Laboratory (Northwest Lipid Laboratories, Seattle, WA) is provided in Section 13 (Laboratory Manual). Review the summary table of specimen types and maximum allowable blood draw volumes for children in Section 13.

Obtaining laboratory specimens is an important component of the study visit; and obtaining fasting blood samples is considered a study priority.

a) If a participant comes for a study visit and refuses to provide a blood sample, the participant should be asked if they are willing to come back to provide a fasting blood sample within the three months of the in-person visit.

b) If a participant comes for a study visit non-fasting, obtain blood and urine samples that do not require fasting (see Section 13) and encourage the participant to re-schedule for a fasting sample within the appropriate time window. If the participant returns for a fasting visit, obtain ALL blood and urine samples, except for DNA.

c) If a participant is willing to schedule a Registry Visit but notifies staff in advance that they will not give a blood sample, staff should use their discretion in scheduling this visit. If they are fairly certain that the participant/parent will not change their mind and provide a blood sample, then the study visit should not be scheduled and it should be coded as "refused".

d) When a participant refuses to provide a blood sample, the visit will be counted as a "partial" visit. The physical examination will be performed and all other data collection forms will be completed. For Registry Visits, these participants will not be included in analyses using biochemical type since blood samples are needed for biochemical typing.

Blood Collection Process

Instructions for completing the Blood Collection Process can be found in Section 13 of the MOP Laboratory Procedures. The Specimen Collection Form outlined below address blood collection (questions 9-13).

Urine Collection Process

Table 12-3: Cohort Visit Urine Collection

Types of urine collections performed	First morning void Random urine collection at in-person visit
Window for urine collections	First morning void: the morning of the in-person visit or on another morning within the three months following the in-person visit. Random urine collection: during the in-person visit or within the three months following the in-person visit.
Screening for transient proteinuria	Questions at the time of the in-person visit and performing the "dipstick" test at the laboratory will markedly reduce the risk of identifying transient proteinuria.

Measurements performed on the first morning void and random urine collections by the laboratory in Seattle	Albumin concentration (mg/dl) Creatinine concentration (mg/dl) Calculation: albumin/creatinine ratio in mg of albumin per mg creatinine
Storage of urines samples	First morning void: five 2 ml aliquots and 2 pellets. Random sample: five 2 ml aliquots
Serum Creatinine	Serum creatinine will be measured by the laboratory and GFR calculated by the Coordinating Center using the CKDEPI formula for ≥ 18 yrs of age and the new Schwartz's equation for < 18 yrs. The estimated GFR is considered a "research value" and will not be reported to the clinical sites.

The goal is to collect and process urine samples for analyses that will provide the opportunity now and in the future to assess the effect of diabetes on the kidney and other bodily functions in SEARCH 3 participants.

Types of urine specimens for collection in SEARCH 3

1. Random void during the in-person research visit.
2. First morning void on the morning of the in-person research visit.

Rationale for types of urine collection

A random void was collected during in-person research visits in SEARCH 1 and 2. To allow longitudinal analyses using comparable specimens, SEARCH 3 will collect a random specimen during the in-person research visit. In addition, due to the fact that 2-5% of adolescents have orthostatic proteinuria, a first morning void will also be collected on the morning of the in-person research visit.

Window for Urine Collections

If the participant does not provide a first morning void at the time of the in-person research visit, the clinical center will attempt to obtain a first morning void within three months of the in-person visit. A three-month window was chosen to allow a comparison between concomitant blood glucose control (hemoglobin A1c).

Screening of urine samples: prevention of detection of transient proteinuria

Transient proteinuria is a normal occurrence and does not reflect pathology. Having procedures in place to limit the detection of transient proteinuria will reduce the false positive rate.

Common causes of transient proteinuria include fever, rigorous exercise, a urinary tract infection, and contamination of the urine sample from menstrual flow. To limit the likelihood of identifying transient proteinuria in either the random or first morning voids, SEARCH will employ the following questions and the laboratory personnel in Seattle will perform the Dipstick test and assess all urine samples for turbidity.

A positive answer to any one of the questions (1-8 on the Specimen Collection form) will result in the clinical site not collecting either urine sample on the day of the in-person visit but collecting both urine samples within three months of the in-person visit.

Specimen Collection Form

The Specimen Collection Form provides information regarding the visit type and participant's status at the time laboratory specimens were obtained. This form should not be confused with shipping and specimen forms provided by the SEARCH Central Laboratory. Data from the Specimen Collection Form will be entered into the SEARCH data entry system; information will remain within this system unless the SEARCH Central Laboratory makes requests for information.

Prior to obtaining laboratory specimen, verify and document that a consent form has been signed for the appropriate specimens, including sample storage and DNA sample collection.

1. Have you had DKA in the last 4 weeks that resulted in hospitalization of had to be treated by IV fluids?
2. Have you had a severe low blood sugar in the past 24 hours that required you to get help (glucagon injection, called 911, went to an emergency room or urgent care center)?
3. Have you had a fever greater than 100 degrees in the past 24 hours?
4. In the past month, have you been told by a doctor that you have a urinary tract infection?
5. Are you currently pregnant? *In some cases, the participant may be uncertain about pregnancy e.g., if their period is late and the possibility exists they are pregnant or they are simply uncertain. Therefore, an option exists for checking* ***"Yes," "No,"*** *or "****Unsure."*** *If the participant responds 'yes' -* ***do not collect a blood or urine specimens at this time and do not complete this form.*** *If the participant is unsure of their pregnancy status -* ***collect blood or urine specimens at this time. Staff should inform the participant if she later finds out that she is pregnant to please let the staff know, and the samples will not be analyzed.***

6. Are you currently menstruating/having your period? *If a female participant is menstruating, a urine specimen should not be obtained at this visit but either rescheduled or obtained as part of another visit.*

7. Were you menstruating when you did your 1st morning void urine collection? *If the participant responds 'yes,' do not send the 1st void urine and reschedule.*

If blood collection is indicated, complete the remainder of the questions.

8. Asks for insulin taken within the previous **4** hours. This does NOT include basal insulin per insulin pump.

   Mark "yes" or "no." If yes, indicate each insulin dose taken by checking the appropriate box. If the 2nd or 3rd box is checked, write in the time of the last dose taken. If no, go to question 9.

9. Asks for other diabetes medications taken within the previous **8** hours.

   Mark "yes" or "no." If yes, ask which medication and mark by the appropriate list on the form; then answer question 9a.

   If any diabetes medicine taken does not appear on the list of insulins or oral diabetes medications, write in the name of the medication in the next section, as well as the time of the last dose taken.

   NOTE: If an unacceptable insulin or oral medication was taken, proceed with the blood draw and try to schedule a fasting re-draw visit.

   9a. If a re-draw visit is necessary, did the participant agree (yes or no)?

10. Ask study personnel to document if the participant had anything to eat or drink within the past **8 hours**.

    10a. If "**Yes**" is selected, ask the participant what they had to eat or drink. Describe what they had to eat or drink and continue to question 10b.

    10b. If participant consumed a non-allowable food or drink, record most recent time.

    10c. If a re-draw visit is necessary, did the participant agree (yes or no)?

    While it is optimal to have the participant in a complete fasting state, it may be impossible to achieve in all circumstances. Therefore, interviewers are requested to determine exactly what types of foods and beverages were consumed in the 8 hours prior to the visit to assess that a threshold of 5 gm of carbohydrates is not exceeded. If the participant consumed a diet beverage, one stick of gum, less than 2 Life Saver candies, 2 Chiclets or 2 Tic Tacs, the laboratory samples can be drawn without requiring a return visit. It is important for the interviewer to prompt the participant to determine the type

and estimated amount of foods and beverages consumed, placing that information in the 'notes' section provided.

Note: If the participant consumed more than the allowable 5 gm of carbohydrates within 8 hours of the visit, obtain blood and urine specimens that do NOT require fasting. Attempt to re-schedule the participant for a fasting visit within a 3 month period. If the participant returns for a fasting visit, obtain ALL blood and urine samples, except DNA.

11. Asks for a glucose meter reading. This test is to be completed after all blood specimen(s) have been collected. Study personnel can use a drop of blood from the blood collection device to apply to the glucose meter strip. This decreases the number of punctures the participant must endure. Example: After drawing blood specimens, the phlebotomist places a drop of blood onto the glucose meter strip and performs a glucose meter check of the participant's blood glucose.
    - o Enter the glucose meter result. Be certain to begin entry with the far right box.

11. Glucose meter reading: ☐☐☐ *(May use drop from blood collected with venipuncture samples)*

If glucose is > 300 mg./dl., perform urinary ketone check and record in 11a.

12. Asks for any symptoms the participant may have. Check all that apply.
13. Asks for additional comments. If yes, write comments in box.
14. Asks for the identification number/code of the person that obtained the specimen. (Each SEARCH staff person is assigned a 3-digit code number.)
15. Asks for the date the specimen(s) was obtained. As in previous examples, use **2** digits for month and date and **4** digits for year.
16. Asks for the time the specimen was obtained. Please remember to check if the specimen was obtained in the morning (AM) or afternoon/evening (PM).

    A positive dipstick or turbidity test will result in the laboratory discarding the sample and reporting this action to the clinical center. The clinical center will attempt to recollect and process a second sample to replace the original sample within three months of the in-person visit.

    Tests performed by the Northwest Lipids Laboratory:

    a. Dipstick for leucocytes: If the reading is "small, moderate, or large" the sample will be discarded.

b. Dipstick for blood: if the "blood reading is "moderate or large" the sample will be discarded. "Small" will not be reported or rejected.

c. Dipstick for nitrites: if the reading is positive the sample will be discarded.

d. Assessment of turbidity: the laboratory personnel will visually inspect all urine samples. Any sample that is considered "turbid" will be assessed by the laboratory personnel. If the laboratory personnel are not able to read 12 point font through the urine sample, the sample will be declared turbid and will be discarded.

NOTE:

- If both the first morning void and the random sample are positive for both leukocytes and nitrites, the participant may be at risk of having a urinary tract infection. When this occurs, the clinical site will notify the participant and/or provider regarding a possible urinary tract infection according to local guidelines.
- If both the first morning void and the random sample are positive for blood, the participant may be at risk of having a urinary tract infection or kidney stones. When this occurs, the clinical site will notify the participant and/or provider regarding a possible medical problem according to local guidelines. (2/13)

Limitations of the screening Process for Transient Proteinuria

SEARCH recognizes that the screening process established by SEARCH will not identify all causes of transient proteinuria. For example, rigorous exercise and recent sexual activity may result in an increase in the amount of albumin measured in the urine. However, due to the inability to identify a standardized question that will effectively screen subjects to eliminate those who have participated in rigorous exercise, and the sensitive nature of information collected regarding sexual activity, SEARCH has chosen to not address these issues, which may result in the identification of some false positive tests for proteinuria.

Tests that will be performed on urine samples by the laboratory:

1. Albumin concentration (mcg/dl)
2. Creatinine concentration (mg/dl)
3. Calculation: Albumin/creatinine ratio in mg of albumin per mg creatinine.

Storage of Urine samples

The clinical center will send the Lab the first morning void urine in a 120 ml transfer tube for the laboratory to process, prepare and store five 2 ml aliquots.

Additionally, the clinical center will send the laboratory the random urine sample in a 10 ml tube for the Lab to process, prepare and store five 2 ml aliquots. Two urine pellets will be obtained and stored from the first morning void. (11/11)

Post-phlebotomy Participant Instructions

- Instruct the Participant to check their blood glucose level (if this has not already been done) and take medication if indicated.
- Provide the Participant with SphygmoCor snack (cohort visit) or breakfast/snack (registry visit).

Note: Follow site-specific guidelines for medication adjustment. Contact the PI or site-designated pediatric endocrinologist if further assistance is needed.

Specimen Shipment - Fresh and Frozen

Instructions for completing the Fresh and Frozen Specimen Shipment Form can be found in Section 13 of the MOP Laboratory Procedures.

Laboratory Result Reporting

Laboratory Reports

Laboratory reports will be distributed to designated center personnel via electronic mail (in the form of PDF files). Laboratory reports have been designed to accommodate both Cohort and Registry Visits.

Each PDF file consists of 2 pages:

- Page 1 of the report is labeled "Provider Report" and provides information including PID, participant results and corresponding reference ranges. Comments regarding specimen collection or shipping may be included if appropriate. This is the page printed and mailed to their health care providers as it includes GAD, IA2 and C-Peptide results or notifies of the urine rejection.

  Example:

Laboratory Comments
1-01-12345 - Poor centrifugation resulting in non-defined gel barrier - sample unusable, new sample required.

  Note: These comments should be carefully reviewed with corrective measures taken.

- Page 2 of the report is labeled "Participant Report" and duplicates page 1, eliminating details on specimen and shipping issues. This is the page printed and mailed to participants.

Study staff will notify participants they are at risk of having a Urinary Tract Infection (UTI) only if BOTH the first morning void and the random sample are positive for BOTH leukocytes and nitrites. Additionally, the individual sites can determine the method in which the results will be conveyed to the participant and providers. (8/12)

Laboratory Report Schedules

Table 12-4 provides the types of reports mentioned above, their associated distribution times, and content. Distribution times are based on normal circumstances. If reports are not received within a reasonable period of time, center personnel should contact the SEARCH Laboratory.

Table 12-4 Laboratory Report Distribution

Report	Report Distribution	Report Contents
Registry	Within 6 weeks of specimen receipt	DAA, HbA1c, fasting lipids, glucose, and C-peptide, and urine albumin and creatinine
Cohort	Within 6 weeks of specimen receipt	HbA1c, fasting lipids and glucose, and urine albumin and creatinine

The only laboratory test determined to have an alert value is triglycerides. ***Laboratory personnel will report triglyceride levels $\geq$ 1000 via electronic mail and facsimile as soon as possible after the test is completed.***

Common Participant Forms

A. Participating Relatives

The Participating Relatives form captures information about the participant's relatives who are participating in SEARCH. The relative's name should be obtained but not entered in the database. Relationship (sibling, full and half brothers and sisters, parent, child, or other) should be recorded on the form. The participating relative's Patient ID number should also be recorded on the form.

B. Contact Information

In order to maintain communications with SEARCH participants and update participants about SEARCH, the Contact Information Form is completed at least annually. Information that is captured includes participant's name, Social Security Number, parent/guardians' names, mailing and email addresses, phone numbers, and permission to contact over the weekend. There are participant and parent versions.

C. Consent Tracking

The Consent Tracking originated as an online form as a means of communicating with the CoC. The form confirms the data elements the participants have consented to use as a part of the SEARCH study. More recently, the online form was made into a hard copy that could be put into the visit packet for the study staff use only and can be used as a prompt for the study staff when entering the data.

D. Unanticipated Occurrence/Event Reporting

Instructions for completing the Unanticipated Occurrence form can be found in Section 17 of the MOP (Patient Safety, Alert Values and Event Reporting and Monitoring).

12.3. PROCEDURES SPECIFIC TO REGISTRY VISITS

Registry Participant Study Forms

(eligible)	Adult Participant	Participant < 18 years	
		Child	Parent
IPS	X		X
Participating Relatives	X		X
Contact Information form	X		X
Medication Inventory (interview style)	X		X
Physical Exam (≥ 3 yrs. of age)	X	X	
Specimen Collection	X	X	

Registry Study Staff Forms

Consent Tracking
Extended Core
Specimen Collection Form
Specimen Shipment - Fresh
Specimen Shipment - Frozen
Unanticipated Occurrence
Unregistration

12.3.1. *Registry Visit Questionnaires*

A. IPS (refer to Section 11 of the MOP for specific details)

If the IPS was completed prior to the study visit, it should be reviewed with the participant and/or parent/legal guardian for accuracy and completion. If the IPS was not completed prior to the visit, it may be completed during the visit. Refer to Section 11 for specific guidance on completion of the IPS.

B. Medication Inventory (Interview)

The medication inventory form was designed to determine all insulin and other medications being used by participants and whether medications were used in the last 2 days.

Question 1: Asks *are you taking prescribed medications, and, if yes, what prescribed medication(s) are you taking?*

Check all insulins and other diabetes medications and write the names of the other medication currently being taken.

Question 2: A*sks that of the medications listed for question 1, which of those have been taken in the past 2 days.* Check yes or no

- If Other Insulin is checked, write in medication name.
- If other injectable medication was used, check box and write name of medication.

At the bottom of the form there is a place to write in other medication being taken including diabetes medications not listed.

Check yes or no if the medication has been taken in the past 2 days.

12.3.2. *Secondary Diabetes Identified During or After an In-person Visit*

Participants identified as having a diagnosis of Other Specific Type of Diabetes during or after an in-person visit will complete the in-person visit including blood and urine specimens. The blood and urine specimens will be processed per protocol procedures. The results of the tests will be transmitted to the participants per study protocol. However, the only data that will be used in the analysis will be the presence/absence of diabetes in the ascertainment year, gender, ethnicity, date of diagnosis, and date of birth. This information will be used to meet one of SEARCH's primary goals describing the prevalence and general characteristics of this type of diabetes (see Appendix D).

12.4. PROCEDURES SPECIFIC TO COHORT VISIT

Cohort Participant Study Forms

(eligible)	Adult Participant		Participant 10-17 years			Participant < 10 years	
			Child	Parent		Child	Parent
CES-D	X		X				
Contact Update	X			X			X
Eating Problems	X		X				
Eye Vision	X			X			X
Family Conflict			X	X			
Family History	X			X			X
Food Frequency	X		X				
Health Questionnaire	X			X			X
Low Blood Sugars	X		X	X			
MNSI	X		X			X	
Participating Relatives	X			X			X
PDQ - quality of life	X		X	X			X
PedsQL (gen. & diab.)	X*		X	X		X	X
Physical Exam (≥ 3 yrs. of age)	X		X			X	
Quality of Care	X			X			X
Specimen Collection	X		X			X	
SphygmoCor	X		X			X	
Supplemental	X		X				
Tanner Stage			X			>8 years	

*Parents of participants who are >18 and <19 yrs. of age will also complete the parent version of the PedsQL

Cohort Study Staff Forms

Consents Tracking
Specimen Collection form
Specimen Shipment - Fresh
Specimen Shipment - Frozen
Unanticipated Occurrence
Medical Record Validation Worksheet

Suggested sequence of visit procedures

A. Single visit

1. Consent; review outline of the visit
2. Participant gives study coordinator the first morning urine collected earlier that day
3. Fasting blood and spot urine
4. Standardized snack/ insulin
5. Cardiac measures
    a. Blood pressure
    b. SphygmoCor
6. All other measures (in any order)
    a. Physical examination
    b. Peripheral neuropathy - MNSI exam and questionnaire
    c. Retinopathy - retinal photos
    d. Questionnaires

B. If two visits are required

Move any of the measures listed in (6) above to another visit

a. Interval between these 2 visits should be < 3 months
b. If interval > 3 months, measure blood pressure and hemoglobin A1c at both visits

Standardized snack

1. The standard snack will be a Nutri-Grain bar and water. Nutri-Grain bars consist of the following macronutrients:
    a. CHO = 24-26 gms.
    b. Fat = 3-4 gms.
    c. Protein = 2 gms.
2. If the participant is allergic to the contents of the Nutri-Grain bar, has celiac disease, or refuses the standard snack for any other reason, the following are *alternatives to the standard snack* - **listed in order of preference:**
    a. Glutino gluten-free breakfast bar

b. Pre-plan with the participant to bring a snack to the visit that has an equivalent amount of CHO and fat

c. Perform SphygmoCor fasting for at least 8 hours overnight without eating the standardized snack. If the participant eats/drinks something else, record what the participant ate (type and amount of food) on the SphygmoCor form. (This would include the treatment of any low blood glucose level.)

3. Sites may provide a meal or an additional snack upon completion of the SphygmoCor or study visit (optional).

12.4.1. *Cohort Visit Procedures*

A. Central Laboratory

Instructions for collecting blood and urine samples can be found in Section 13 (Central Laboratory) of the MOP.

B. Physical Measures

Instructions for collecting height, weight, waist, blood pressure, and acanthosis nigricans can be found in Section 12.2 of the MOP.

C. Retinopathy

Instructions for collecting Retinal Photos can be found in Section 14 (Retinopathy) of the MOP.

D. SphygmoCor

Instructions for collecting SphygmoCor measures can be found in Section 15 (SphygmoCor) of the MOP.

E. Michigan Neuropathy Screening Instrument (MNSI)

Instructions for collecting MNSI measures can be found in Section 16 (MNSI) of the MOP.

12.4.2. *Cohort Visit Questionnaires*

A. Depression - CES-D Form (Age 10 & older)

Scientific Rationale

Depression among adolescents is an important cause of morbidity. Almost one in five teens will become depressed sometime in adolescence.[10] Poorer health status can be associated with depression and depression affects functioning on multiple levels. Thus, for diabetes, depression represents an important co-morbidity, which can impact on adherence to treatment regimens and progression of disease. For Type 2 diabetes, it is unclear if depression represents a risk factor for diabetes, as

well. If depression is associated with incidence and persistence of obesity, it could indirectly impact on development of diabetes.

Measurement Approach

Since diagnostic interviewing is time and labor intensive, most studies measure depressive symptoms. No one scale adequately measures depressive symptoms among children, adolescents, and young adults. The Centers for Epidemiologic Study - Depression Scale (CES-D) has been widely used among adolescents.[11] The CES-D gives flexibility with regard to analytic strategy by working as both a continuous and a dichotomous measure. It can be used as a continuous measure of depressive symptoms or scores can be dichotomized at cut points that maximize the sensitivity and specificity for predicting major depressive disorder (MDD).[11,12] The cut points for predicting MDD differ for teens and adults. It is well received by subjects and easy to complete.

- The depression questions are directed toward the participant.
- Data for the CES-D will be collected by self-report.
- The cover sheet provides information to the participant about:
  - Why the form is being used (to determine how they felt or behaved during the past week)
  - What the response selections will be (rarely, some of the time, occasionally, or most of the time), and
  - If there is potential for the participant to require treatment, their information will be shared with their Parent/Legal Guardian.

Response Selections

The following categories are presented as response selections for the CESD:

Response categories are:

0=Rarely or none of the time (less than once per week)

1=Some or a little of the time (1-2 days per week)

2=Occasionally or a moderate amount of the time (3-4 days per week)

3=Most or all of the time (5-7 days per week)

However on questions # the scale is reversed.

Participant Scoring and Action Values

Participant scores are determined by adding the values of all 20 responses. **Action values are: ≥ 24 for subjects < 18 yrs. of age (both males and females) and ≥ 16**

for subjects 18 yrs. of age or older. A scoring grid provided at each site will allow rapid scoring of the CES-D to determine if an Action Value has been reached. A laminated 'overlay' of the CES-D is provided that will align with the participant's response to each question. The overlay has the appropriate score for each question placed under each the response set. Using an erasable marker, place the score for a particular response in the unshaded box on the right of the answer set. When all response values have been entered, subtotal each column and place column totals at the bottom right corner of the overlay. Add the column subtotals to get the total score.

B. Contact Update Form

In order to maintain communications with SEARCH participants and update participants about SEARCH, the Contact Information Form is completed at least annually. Information that is captured includes participant's name, Social Security Number, parent/guardians' names, mailing and email addresses, phone numbers, and permission to contact over the weekend. There are participant and parent versions.

C. Diabetes Eating Problem Survey (DEPS-R) (Age 10 & older)

Overview

The DEPS-R is a 17-item diabetes-specific self-report screening measure for disordered eating for cohort participants ages 10 and over that use insulin to treat their diabetes. The survey should be self-administered. The first question asks whether or not the participant takes insulin. If yes, they should complete the remainder of the form. If no, the form should not be completed.

The 16 questions are a series of questions related to a variety of attitudes and behaviors regarding diabetes management. For each statement, the participant should think about their attitudes and behaviors in the past month. They should check one answer that indicates how often this statement was true. The response set includes "0=Never, 1=Rarely, 2=Sometimes, 3=Often, 4=Usually, 5=Always."

The last question asks if the participant takes less insulin than he/she should. The participant should mark yes or no.

D. Eye Vision

The Eye Vision form asks if the participant has an optometrist or ophthalmologist that he/she sees. If the participant sees an optometrist or ophthalmologist, the name, phone number, and mailing address are recorded on the form. The form also captures if laser treatment or injections due to diabetic retinopathy have been administered. In the For Study Use Only box, staff should record if there were any

difficulties in obtaining the retinal images. If there were difficulties, the main reason for the difficulty should be checked (camera, participant, operator, or other).

E. Diabetes Related Family Conflict Scale (Parent and Participant 10-17)

Overview

The Family Conflict Scale is a 19 question survey with an added question pertaining to exercise that will be used to assess diabetes-related family conflict, which has been proposed as a possible mediator in the relationship between primary exposures (e.g., motivational interviewing, problem-solving training, family communication counseling, use of technologies) and the primary outcome (e.g., HbA1c). There is a parent version and a participant version to be self-administered for ages 10-17 and should take approximately 5 minutes to complete.

Questionnaire Administration

All questions pertain to how much the primary caregiver and the SEARCH participant has argued with each other in the past month about various diabetes-specific prompts. For each question, the respondent should mark "1=Almost Never," "2=Sometimes," or "3=Almost Always" in response to the question as to how much they argue with each other about the given prompt.

Question 20 (regarding exercise) has not been validated at present but there are plans to do such and add as a standardized survey.

F. Family Medical History Form - Interview

Sites should print out the previously completed Family Medical History form from the website prior to the visit. Review the completed form with the participant and ask for any updates.

Overview

The Family Medical History questions are designed to determine:

- the number, gender, multiple birth status and age of family members
- a history of diabetes, and some markers for type of diabetes (age of onset)
- a history of cancer
- a history of high blood pressure, stroke, and heart attack in selected members, and
- if anyone had premature heart disease (by age of onset of heart attack).

A general family history will be developed to facilitate possible future family studies.

Information will be gathered regarding general health issues of the participant's parents, all siblings, and maternal and paternal grandparents. Family history of diabetes will be useful to examine in relationship to type of diabetes, once determined for cases. It will not be easy to classify type of diabetes among family members by history. Only age at diabetes onset will be collected, since use of medications will mostly be unknown and not easily collected from family members. In addition, these data will assist in classifying families with apparent MODY [10,11] and allow for efficient selection of those for further genetic testing, when available.

Since cardiovascular disease (CVD) risk factors are collected on cases, examination of risk factor levels and prevalence of multiple risk factors by family history of CVD will be useful descriptively. It is expected that CVD risk factors (including insulin levels) will cluster in cases with multiple affected family members and/or premature CVD in parents or grandparents [9,12-13; 1,5,9,14-17]. It is also likely that the association of CVD risk factors will differ in type 1 and type 2 cases (likely higher in type 2 cases) [3,5,18].

Question 1: Asks if the participant has siblings. The <u>total number of brothers and sisters</u> is asked to determine the amount of information to be collected. Use this field to verify that all sibs have been included.

- For each sibling, the same questions will be asked. They are described here only once.
- The information is placed in tabular form to assist the interviewer rapidly document the data.
- Each section or row of the table is provided with a number for easier identification of the field. They are listed as:

	Need to Complete	1. Is this person alive now?			2. Current age, or if dead, age at death	3. Year of birth	4. Hx of Diabetes			5. If yes, Age at Dx	6. Hx of High Blood Pressure		
Brother 1	☐	Yes ☐	No ☐	Dk ☐	☐☐	☐☐☐☐	Yes ☐	No ☐	Dk ☐	☐☐	Yes ☐	No ☐	Dk ☐
Brother 2	☐	Yes ☐	No ☐	Dk ☐	☐☐	☐☐☐☐	Yes ☐	No ☐	Dk ☐	☐☐	Yes ☐	No ☐	Dk ☐

<u>Sibling History</u>

SEARCH is interested in the participant's biologic brothers and sisters, not step brothers and sisters.

- Biologic siblings can be full siblings (brothers or sisters who have the same natural mother and father) or half siblings (brothers or sisters who have the same natural mother or father with the participant).

- Stepbrothers and sisters are those who have a different natural mother and a different natural father then the participant.

As the interviewer, you may wish to document the sibling's name ***on a separate sheet of paper - do not place sibling names on the form***. Only use the FIRST name for ease in discussing the sibling in question. It is not entered into the database. Use it to say - "Now, thinking about NAME, <e.g. John>…" When you determine the number of brothers the participant has - place a check mark in a corresponding "Need to Complete" section. Example: If the participant has 2 bothers, place a check mark in the "Need to Complete" section for *Brother 1* and *Brother 2*. Similar rules follow for the number of sisters.

Section 1. This section asks if the sibling is currently living. Check the appropriate box.

Section 2. Asks for the sibling's current age in years or, if not living, their age at death.

Section 3. Year of Birth: Include 4 digits: 19XX or 20XX. If date of birth is not known, enter **1800.**

Section 4. History of diabetes. Ask if <NAME> was ever told by a health care provider that they had diabetes.

- Respond **"Yes," "No"** or **"Don't know."**

Section 5. If yes, age at diagnosis. If "Yes" is checked, ask the age of the sibling at the time of diagnosis. If the respondent in uncertain, ask them to estimate the age to the best of their ability. If the information is unknown at the time, enter **[-9]**.

If the respondent does not know the actual age, ask them to estimate or "guess about the age <PARTICIPANT NAME> was diagnosed with diabetes". If they respond: "sometime between age X and Y" - enter approximate midpoint age.

Examples: Between 5 and 10: enter 7

Between 15 and 19: enter 17

Note: If the respondent reports gestational diabetes in a family member, enter "No". Staff should not probe for gestational diabetes.

Section 6. High blood pressure? Ask if a health care provider told them if <NAME> had high blood pressure (or hypertension). Do not ask if they took medication for it. If they say, "<NAME> took high blood pressure pills, but I don't know if they had high blood pressure" - consider this a "yes" response.

- Respond **"Yes," "No"** or **"Don't know."**

Complete the same questions for each sibling, and when finished, check that all brothers and sisters have been included. Verify that the number entered in question 1 is the same as the total siblings entered. If not, clarify with the respondent that all siblings have been entered.

Other Relatives

SEARCH is interested in the participant's biologic Parents and Grandparents, not step Parents or Grandparents.

The next set of questions is about the PARTICIPANT'S MOTHER, then about their MOTHER'S PARENTS or the participant's Maternal Grandparents. Once information about that PARTICIPANT'S MOTHER'S family is gathered, the same questions are asked about the FATHER and the FATHER'S PARENTS, or the participant's Paternal Grandparents. All questions are the same for each person and are described only once.

This section of the form, similar to the Sibling section, divides each row into sections. They are listed as:

	1. Is this person alive now?			2. Current Age or if dead, Age at Death?	3. Year of Birth	4. Hx of Diabetes			5. If yes, Age at Dx	6. Hx of High Blood Pressure			7. Hx of Heart Attack			8. If yes, Age at Dx	9. Hx of Stroke			10. If yes, Age at Dx	11. Hx of cancer (not skin cancer)		
Mother	Yes ☐	No ☐	Dk ☐	☐☐☐	☐☐☐☐	Yes ☐	No ☐	Dk ☐	☐☐	Yes ☐	No ☐	Dk ☐	Yes ☐	No ☐	Dk ☐	☐☐	Yes ☐	No ☐	Dk ☐	☐☐	Yes ☐	No ☐	Dk ☐
Mother's Father	Yes ☐	No ☐	Dk ☐	☐☐☐	☐☐☐☐	Yes ☐	No ☐	Dk ☐	☐☐	Yes ☐	No ☐	Dk ☐	Yes ☐	No ☐	Dk ☐	☐☐	Yes ☐	No ☐	Dk ☐	☐☐	Yes ☐	No ☐	Dk ☐

If information is not available about a biologic parent or grandparent, check the box for "Don't Know" [DK] as appropriate. In the unusual situation where they know about the grandparents of the biologic mother or father, enter the data as reported, even though the mother or father's information will be entered "Don't Know." Do not leave fields blank.

Section 1. Ask if this family member (<NAME>) is still alive, or if he/she has died.

- Respond **"Yes," "No"** or **"Don't know."**

Section 2. Current age or if deceased, age at death. If they know the date of birth accurately, this field may be left blank. If the information in unknown at the time, enter **[-9]**.

Section 3. Year of Birth. Include 4 digits: 19XX or 20XX. If date of birth is not known, enter **1800.**

Section 4. History of diabetes? Ask if the respondent knows if this relative has a history of diabetes.

- Respond **"Yes," "No"** or **"Don't know."**

  If YES, ask about the age of this relative at the time of diagnosis and record the age.

Section 5. Age at diagnosis. Document the age, in years, at the time of diagnosis. Respond:

00 = diagnosis before first birthday

01-98 = diagnosis age in years

If the information in unknown at the time, enter **[-9]**.

If the respondent does not know the actual age, ask them to estimate or "guess about the age <PARTICIPANT NAME> was diagnosed with diabetes". If they respond: "sometime between age X and Y" - enter approximate midpoint age.

Examples: Between 5 and 10: enter 7

Between 15 and 19: enter 17

Section 6. High blood pressure? Ask if the respondent knows if this family member had high blood pressure (or hypertension). Do not ask if they took medication for it. If they say, "<NAME> took high blood pressure pills, but I don't know if they had high blood pressure" - consider this a "yes" response.

- Respond **"Yes," "No"** or **"Don't know."**

Section 7. Heart Attack. Ask if the respondent knows if this family member had a heart attack. If needed, probes include: myocardial infarction. Do not include if only angina or chest pain are reported.

- Respond **"Yes," "No"** or **"Don't know."**

Section 8. If yes, ask the Age of first heart attack. If participant or parent knows of more than one, attempt to identify age of first heart attack.

Section 9. Stroke. Ask if the respondent knows if this family member had a stroke. If needed, probes include: blood clot on the brain, brain hemorrhage, brain attack, or brain infarct. **Please note, if the participant states their family member had/has "TIAs" (transient ischemic attacks) this is NOT to be considered a stroke and the response should be "NO."**

- Respond **"Yes," "No"** or **"Don't know."**

Section 10. If the answer to Section 9 is yes, ask the Age at first stroke. If participant or parent knows of more than one, attempt to identify age of **first stroke**.

Section 11. History of Cancer (other than skin cancer). Ask if the respondent knows if this family member had cancer - other than skin cancer. **Please note that melanoma is not to be considered a skin cancer. Therefore, if the participant states a family member had melanoma, the documented answer to this question would be "Yes."**

- Respond **"Yes," "No"** or **"Don't know."**

Repeat these questions for other family members.

History of Gestational Diabetes for the Family Medical History Form

- Gestational diabetes is an "Other Type of Diabetes." SEARCH does not collect gestational diabetes history information on study participants unless the hyperglycemic state continues after the pregnancy. As such, SEARCH will not collect this information on participant relatives.
- For a participant who has siblings and/or other relatives, the participant should be asked if the sibling(s) and/or other relative(s) were ever told by a health care provider that they had diabetes. The participant should respond, "Yes", "No", or "don't know."
- If the participant reports that a family member had gestational diabetes, the form should be marked as "No." Staff should not probe for gestational diabetes.

G. Food Frequency Questionnaire (Age 10 & older)

Overview

Many dietary factors may be important in the development of risk factors for atherosclerosis in persons with type 2 diabetes, either as a function of energy balance or through metabolic pathways that are independent of obesity. Specific nutrients of interest include total caloric intake, dietary fats (total fat and specific fatty acids), and carbohydrates. In addition, there is increasing recognition of the potential health effects of whole foods, food groups, and other dimensions of dietary patterns. Despite the widely recognized importance of diet in the management of diabetes, no study to date has systematically documented usual dietary intake in a large, diverse sample of youth with diabetes. The potential role of dietary intake in development of risk factors for cardiovascular disease (particularly dyslipidemia) has recently been extensively reviewed and will not be repeated here [18]. This technical review provided the basis for the recently

published Evidence-Based Nutrition Principles and Recommendations for the Treatment and Prevention of Diabetes and Related Complications [11].

Research Questions relate to risk factors for chronic complications and to processes of care, as follows:

Dietary intake in relation to risk factors for macrovascular complications

- What is the association of carbohydrate intake on plasma triglyceride concentration among youth with diabetes?
  - Does this differ according to dietary intake of fiber or whole grain foods?
  - Does this differ according to current level of obesity, or according to change in BMI from the time of diagnosis?
- What is the association of fat intake (total fat and saturated fat) on plasma LDL concentration among youth with diabetes?
- What is the association of total fat intake with current level of obesity? What is the association of fat intake with BMI change from the time of diagnosis?

Dietary intake in relation to processes of care

- How does the reported nutritional content of the diet (specifically percent calories from macronutrients) compare to current ADA recommendations for nutrition in individuals with diabetes? Does this vary according to other aspects of diabetes self-management (e.g., frequency of HbA1c testing, SBGM).

Methodology

The diet assessment questionnaire is a staff assisted, self-administered survey of the dietary habits of SEARCH participants, limited to participants age 10 years and older. The SEARCH dietary assessment is designed to facilitate analysis of specific nutrients and whole foods, as well as overall dietary patterns. The diet assessment will be used at the Cohort Study Visit. It is modified from the Kids' Food Questionnaire, developed by Gladys Block and validated in children as young as 8 years old, including African American youth living in a low-income neighborhood. Modifications include addition of selected foods likely to be important to nutrient intake in the ethnically and regionally diverse SEARCH population, as well as consideration of the age range of SEARCH. The original Kids' Food Questionnaire included about 75 food lines; the SEARCH form includes about 85 food lines. These additions were based primarily on foods identified for inclusion for the NIH/NIDDK-funded Diabetes Prevention Program that has similar diversity (albeit an adult population). Other modifications include

a small number of questions designed to more fully understand whether the period of recall (one week) reflects "usual" intake for the individual, use of dietary supplements and use of low-fat products.

Note that the management of the dietary assessment will be directed by the Coordinating Center. Questions regarding either administration of the questionnaire or management of the forms should be directed to:

PI: Elizabeth (Beth) Mayer-Davis, PhD, MSPH, RD
Phone: 919-966-1991
Fax: 919-843-2011

Questionnaire Submission: Once completed, unlike other SEARCH forms, the Diet forms will be sent to the CoC for processing, and quality control procedures. To ensure that forms are not lost, and to avoid the need to make copies of completed forms at the sites,

FORMS MUST BE SENT BY FEDERAL EXPRESS, WITH A TRACKING NUMBER AVAILABLE

(You do not need to use overnight delivery; 2-day delivery is fine)

Before mailing forms, fax or email a log sheet (to be provided by the DAC) that specifies which forms (by participant ID) are being sent. This is used to quickly identify missing batches and missing individual forms. Please note that acrostics should not be included on the SEARCH Diet Assessment forms.

Mail Forms To:

Nora C. Fino
Wake Forest School of Medicine
Division of Public Health Sciences
Medical Center Blvd.
Winston-Salem, NC 27157-1063
Phone: 336.713.1469
Email: nfitzger@wakehealth.edu

Forms should be mailed **once** a month.

Instructions for Administration of the Diet Interview

The goal of the Food Questionnaire is to obtain information about **usual** dietary practices of the participants, and to do so consistently at all clinical centers. Note that the form is called the "Food Questionnaire" rather than the "Diet Questionnaire" or "Nutrition Questionnaire". This is to minimize bias related to reporting of intake that is considered desirable rather than focusing on food actually eaten. Ideally, for a hypothetical participant, the same results would be obtained no matter who is administering the questionnaire, how it is administered (self or interviewer), when it is administered, or where it is administered. However, in any multi-center study, differences in the administration of a questionnaire will exist among staff and interviewers, among centers and over time. These differences can seriously bias results of statistical analyses. Thus, standardization of the administration of the Food Questionnaires is critical to the data quality. The DAC has established certification guidelines (see Training and Certification) and will maintain listings of certified staff and interviewers.

The mode of administration of the SEARCH diet assessment will be **staff-assisted self-administration**. "Staff assisted" refers to the process of providing instruction to the participant, rather than simply handing a blank form to the participant. It is important to provide the participant with instructions for completing the form and answer any questions that may be asked (see below for guidelines). If, due to participant circumstances (such as literacy or vision impairment), the form must be completed as an interview, this is acceptable (see instructions for interview administration, below).

Instructions for the participants to complete the form on their own

A simple, clear introduction is extremely important to obtaining valid information from the questionnaire. Instructions are included throughout the form. Do not overwhelm the participant with too much detail! **Keep it simple.**

Do Not Give The Form To The Participant And Try To Read It To Them At The Same Time. Generally, This Is A Poor Interview Style Because Participants Cannot Read And Pay Attention To You At The Same Time

- Present the form to the participant and let them know that you will take a few minutes to explain how to fill out the form.

- Read the information on page 2. Be sure to write in your name so that the participant is comfortable going to you by name to ask questions. If the form goes home, be sure to provide a stamped envelope for them to use to return the form. Write down the date the form is due (one week from giving out the form), and be sure you make this clear to the participant.
- Important Note: It is up to the SEARCH staff and participant to determine if the form is to be completed by the participant while they are in the clinic, or whether the participant will take the form home, complete it there, and return it by mail (or in person). However, from our experience, it is much better to have the form completed in clinic if possible. This allows easy access to study staff should any questions arise, and ensures that the form is returned in a timely manner, with minimal staff effort in follow-up. This also allows for the form edit to be done quickly and any omissions or clarifications to be obtained with the participant still present in clinic.
- Encourage the participant to be careful to mark the appropriate bubble and to fill in the bubbles completely using a #2 pencil. Use the first three short questions (top of page 3) to demonstrate filling in the bubbles correctly.
- Continue reading instructions on page 3.
- When you say (on page 3), "…sometimes using the pictures at the back of the form," go over portion size responses located as the last page of the form. These are self-explanatory. Indicate that for each food, the participant will be asked how much they ate. When the form tells them to use the pictures, this is what they turn to for pictures of different amounts of food, either on plates or in bowls. When the participant is working on the form, they can pull out this page of pictures and keep it beside the rest of the booklet (just be careful not to lose the picture page if they are working at home). This approach is designed intentionally to provide only limited information about portion size. Be careful to avoid bogging down in detail here!
- Turn to page 4 of the form.
- To help participants feel oriented to the form, tell them the items are grouped by type of food.
- Remind participants to think of foods eaten at home and away from home. Remind them to include both meals and snacks.
- Emphasize completeness and that no line should remain blank. The participant should check "no" rather than simply skip foods he or she rarely or never eats.

- Inform participants that if they don't eat a particular food, they may leave the serving size blank.
- Point out open-ended section (on page 16), to record anything else eaten every day or almost every day.
- Point out the few additional questions at the end.
- Point out the space to let us know anything else they would like us to know about their usual dietary practices.
- Note that the last page is for clinic use only.
- Ask if there are any questions. Give the form to the participants and let them know they may call anytime if questions arise.

Tracking Self-Administered Forms

Encourage the prompt return of the questionnaire. If more than one week has passed, and the form has not been returned, call the participant at least once daily until you have been in contact with the participant and arrangements have been made for the return of the form.

If you suspect that the participant is unlikely, unwilling or unable to complete the form, you may collect the data over the phone (see instructions for interviewing, below).

Notes on General Interviewing Style and Cultural Sensitivity

The skill and consistency of the interviewers will strongly influence the quality of the dietary data. Please review the general interviewing techniques provided at the beginning of the SEARCH MOP. In particular, remember to establish a non-judgmental atmosphere. You are not here to evaluate dietary intake. You are here to facilitate accurate reporting of dietary behaviors by the participant, and to accurately record the participants' responses.

SEARCH has a major advantage because of the diverse population included across the clinical centers. The nutrition interview includes a wide variety of foods that are likely to contribute substantially to nutrient intake within the various subgroups of ethnicity and geographic region included in the study. *Keep in mind: the only important foods to consider in this dietary assessment are those that contribute substantially to overall usual nutrient intake.* Foods that are important from a cultural perspective but which are eaten only infrequently (e.g., special holiday foods) generally do not contribute substantially to usual nutrient intake. Therefore, such foods have not been included in the interview.

It is necessary to achieve a balance between cultural sensitivity, sensitivity to the individual, and standardization. For the purpose of standardization, each diet interviewer must include (by saying out loud) the complete listing of all foods when interviewing study participants. For purposes of sensitivity to individual dietary choices and to culture, the diet interviewer needs to listen carefully to the participant, and can spending relatively more time on foods consumed more frequently and less time on foods rarely consumed. For example, if the participant is unfamiliar with a particular food, it is unlikely to be an important source of nutrients. Minimize time on these items.

However, DO NOT ASSUME that you can anticipate what a particular individual may eat. In today's cities, ethnic foods are easily available to all. Therefore, interviewers need to:

- Be familiar with all foods on the FFQ form.
- Be familiar with the foods common in your community.
- Be aware of possible language barriers.
- Be aware of cultural and/or personal differences in communication style.
- Note that if a participant reports a food and you do not know what the food is, ask the participant to describe it, including major ingredients and cooking method. Do not assume that the DAC will know what it is! Write the information down so that we can determine how to code the food.
- Be aware of language differences among participants. Have a bilingual conversation as needed.
- Be aware that some foods may only be known in the original language (e.g., frijoles for beans).
- Be aware of literacy level and level of understanding when interviewing participants. The interview scores at about the 8th grade level (lower for instructions only). However, this assumes English as a first language.

Specific Instructions for Conducting the Diet Interview

Introduction of the Interview

Use the text on the form as a general guide to briefly introduce the form.

NOTE: The exact wording on the form is for the benefit of the participants who will complete this as a self-administered form. Adjust the language as appropriate for interviewer-administration. For example, instead of "tell us how often…," say, "I will ask you how often…"

General Questions

General questions such as meal and snack frequency are designed to help orient the participants' thoughts to the topic of what he/she ate last week. They are also used to understand aspects of dietary behaviors.

Meal and Snack Frequency

If the participant gives a range, take the midpoint and confirm with the participant. For example, for a response of "2 to 4," the interviewer would ask, "Would you say 3 is a good average?" For a response like 2-3, ask, "Is it more often 2 or more often 3 snacks a day?" If the participant insists on 2.5, code it as 3 (i.e., round up). If meal or snack frequency is very different for days they work vs. days off, ask about "most" days.

Frequency of School Lunch (or Breakfast)

This generally refers to cafeteria-style service. It does not include taking breakfast or lunch from home.

Restaurant Frequency

This includes fast foods, "take-out", and home delivery of whole meals, including pizza if this constitutes a meal.

Body of Interview: Food Frequency

Note, during an interview process or if the participant has questions relating to a particular food, first ask if the participant ate a particular food at all. Show the participant the cue card for frequency (1/week….up to every day) and review all responses. Keep this cue card out and easily available.

Body of Interview: Portion Size

Simply note that for each type of food, you will be asking about how much the participant ate. See Instructions for Self-Administered Forms, regarding portion size.

> **NOTE**: *Do Not* get bogged down in excessive detail -- we are not expecting exact reporting of portion sizes. We simply want the participant to tell us the general ballpark of their typical portion size for each line item. The approaches to portion size are explained above.

Food List

There are headings throughout the form to identify the type of foods to be queried. The first section is "Breakfast Foods". Let the participant know the

name of the section to help him/her orient their thinking. For example, say, "First, we'll go over fruits and juices."

For each line item, in general, you should read all items on the list. There are some items that will almost never apply to certain centers or to certain participants. It is sometimes appropriate to use some judgment here, but remember that consistent use of the interview across centers is vitally important. As an example, if a person says that she is a vegetarian, you should still confirm in the food list section that she does not eat any type of beef, then any type of pork, then any type of chicken, etc. You would not need to mention each type of beef within the roast beef line item. Inclusion of all line items is necessary to avoid missing the particular food choices that may enable us to discern relatively small but potentially important differences in nutrient intake between individuals. **The key thing to remember is not to assume too much.**

Most items in the meat, fish and poultry section are main dish items. While you can check to make sure that the total number of main dishes makes some sense, remember that many people do have eating habits that may seem unusual to you. Probe further if you hear something that seems highly unlikely, but don't try to get answers based on your expectations of food habits.

Beverages

IMPORTANT: When you review the response set for beverages and you are using cue cards, be sure to remove the old set from sight and point to the new set of answers to avoid confusion. Be sure that the frequency of milk as a beverage <u>does not</u> include milk used on cereal or in coffee or tea.

If a participant thinks of additional information during the interview related to a food item you have already coded, go ahead and go back to that item while the participant is thinking of it and modify the answer as needed.

Food Preparation

Tell the participant that you will now ask a few more questions about their diet. Review responses (never eat the food, seldom or never, sometimes, often or always). For the questions about type of fat used, the scanner will accept either one or two answers. If the participant only uses one type of fat, if at all, fill in only one bubble. If the participant uses more than two types of fat, record only the two that he uses most frequently.

Additional Foods (page 16)

Ask the participant if there are any other foods that they eat every day or almost every day. These should be foods that have not been reported previously! Give the participant a moment to think before moving on. For any foods reported at this time that are included elsewhere on the form, incorporate them into the main body of the questionnaire as appropriate, including frequency and portion size. Record any additional foods on page 16. Be sure items are legible and the frequency is complete. For mixed dishes, be sure main ingredients and preparation method is obvious or noted. The DAC will code these items.

Comment Section

Sometimes a participant will tell you something about his/her diet that is important to him/her but which is not appropriate for inclusion on the interview form. For example, a participant may note that she/he doesn't like vegetables. You can note these things in the comment section so that the participant knows you are listening to him/her and are ready to move on. These comments generally require no further review. (See Section below on editing.)

Checking/Editing the Completed Form (whether interview or self-administered)

When the questionnaire is returned (or the interview is complete) spend a few minutes (usually two to five minutes) checking over the questionnaire. Ideally, you will do this while the study participant is still there. If the questionnaire is returned by mail, check the form as soon as possible in case clarification is needed. Do not mail the form to the DAC unit until editing is complete**. The goal is to identify obvious omissions or errors, NOT to judge the quality of the participant's diet.**

- Make sure the information in the "For Clinic Use Only" is complete and correct.
- Check for omissions - skipped foods, missing information.
- If there is an occasional missing line within the list of foods, you do not need to contact the participant. If three or more items in a row are missing, contact the participant to complete the items.
- If any other question has been skipped, contact the participant.
- Check for extremely unlikely frequencies, such as "every day" for an entire page of main dishes. Contact the participant to confirm such

responses, and, if needed, provide a comment in the "For Clinic Use Only" box (see below).

- If other foods are reported in the open-ended question, be sure these are described (e.g., a recognizable name of food, or if a mixed dish, the main ingredients and cooking method).
- Complete the For Clinic Use Only review flags. These include:
  - "DAC review needed for coding". Mark this as "yes" if something has been written in on page 16.
  - "Comment" (yes / no). Mark this as "yes" if there is other information regarding reported foods or questionable reliability of the form that may impact on data quality. Briefly describe your question or comment. If you are unsure, feel free to contact the DAC directly (contact information above) and we will respond very quickly to your inquiry.

H. Health Questionnaire - Self Administered (Participant and Parent Version)

Overview

An individual's medical history provides a map with multiple factors that influence the evolution of diabetes. The Health Questionnaire (HQ) will provide information regarding the medical background of participants in the SEARCH study. Areas reviewed in the HQ focus on the participant's medical history, diabetes treatment modalities, concomitant medications, diabetes education, status of diabetes care, and information regarding the type of health care provider and household resources for diabetes treatment.

Methodology

The Health Questionnaire is a self-administered survey designed to assist in the analysis of factors affecting the onset or treatment of diabetes. Some questions included in the Health Questionnaire are standardized questions from existing diabetes and youth studies, e.g., DCCT, YRBSS. Through the question standardization it is anticipated that data collected from SEARCH participants will be compared to other diabetes and youth databases.

I. Low Blood Sugar Survey (3 versions: ages 10-17; 18 or older; & parent)

Overview

The low blood sugar survey was designed to learn more about behaviors employed by participants to guard against hypoglycemia in the last 6 months and the concern or worry they may have about experiencing a hypoglycemic episode. The survey is designed to be self-administered. There are three versions of the form: one for

parent/guardian (25 questions), one for children and teens ages 10-17 years (32 questions), and one for adult participants who are 18 years or older (33 questions).

Form Questions

Part I of the questionnaire consists of a list of strategies a participant or parent might use to avoid hypoglycemia and its consequences. There are 10 behaviors (questions 1–10) listed on the child/teen and the parent versions. There are 15 behaviors (questions 1-15) listed on the adult version. The respondent is to indicate how often he/she employed that strategy using the given scale. The participant versions include the scale of 0 to 4 scale where 0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, and 4 = Almost Always. The parent version includes the scale of 1 to 5 where 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Very Often. The answer is indicated by circling the number along the scale that best describes the person's behaviors over the last 6 months. The child/teen version of the form offers a space at the end of Part I for the participant to write in any other things he/she may be doing to guard against hypoglycemia.

The second part of the survey consists of a list of concerns a participant or parent might have about developing hypoglycemia. There are 15 concerns listed (questions 11 - 25) in the child/teen and parent versions. There are 18 concerns (questions 16 - 33) listed in the adult version. The participant is to indicate how often he/she is worried about the specified concern on the scale as described above. The participant circles the number along the scale that best describes his/her level of concern. The child/teen version offers a space at the end of the list to write in other things they may be worried about concerning low blood sugars. The child/teen version of the form has a second part (ques. 26 - 32) to Part II that continues to probe about concerns and worries of low blood sugar. The respondent has the choice of five responses: Never, 1-2 times, 3-6 times, 7-11 times or 12 or more times.

J. Michigan Neuropathy Screening Instrument (MNSI)

(See Section 16 of the MOP for specific details)

Overview

The Michigan Neuropathy Screening Instrument is used to assess the presence of peripheral diabetic neuropathy and is conducted at the cohort visit. The MNSI consists of two parts: Part A is a brief questionnaire about symptoms of peripheral neuropathy, and Part B includes a physical examination of the feet.

Part A: Neuropathic History Questionnaire

The MNSI questionnaire is designed to be a self-administered form and consists of 15 questions asking about the presence or absence of peripheral neuropathy

symptoms in the participant's legs or feet. The allowed response to this series of questions is YES or NO only. The participant should place an X in the box that best describes the feeling in his/her legs and feet.

Upon review of the form, staff should pay special attention to the answers to questions 7 and 13 as these are sometimes inadvertently marked NO since the absence of symptoms for the other questions on the form is indicated with a NO answer. If the answer to question 7 or 13 is marked NO, please repeat the question to the participant as it is written to ensure that they answered in the way they intended. If they still answer NO, then leave the answer. However, if they indicate that they should have answered YES, correct the answer by putting one line through the unintended answer and place an X in the correct box. Initial and date the change on the form.

Part B: Physical Assessment

Part B of the MNSI form is the data collection sheet for the physical examination of both feet that includes the following components: 1) foot inspection, 2) ankle reflexes, 3) vibration sensation, and 4) monofilament testing for touch sensation.

Each of the five questions on the form allows for recording of the findings for the right foot and left foot and answers may vary based on the measure and the foot tested.

Question 1 concerns the appearance of the foot. If no abnormalities are observed upon inspection of the foot, question 1a should be marked YES. However, if abnormalities are observed, then question 1a should be marked NO and question 1b should be completed by marking all the abnormalities from the listing that were evident. Specific abnormalities listed are Deformities; Dry skin, callous; Infection; Fissure; and Other.

A description and examples of each abnormality follow:

- Deformities (hallux valgus or bunion, claw foot, Charcot foot, hammer toe);
- Dry skin, callous (thick, flaky, leathery skin often localized over a pressure point, not evenly distributed). Common dry skin that looks like it could be resolved by an application of skin lotion should not be marked as an abnormality here;
- Infection (Athlete's Foot as evidenced by red, flaky, macerated skin between and around the toes or other infection marked by pus and irritated skin);
- Fissure (deep split in the skin);

- Other (specify).

If "Other" is marked, the examiner should write in the abnormality on the line provided. Possible observances that might be classified as "Other" are toenail fungus, amputation, and fracture.

Question 2 concerns the presence or absence of ulceration and is answered by marking the correct box (Absent or Present) for each foot. Superficial scrapes and cuts of the skin that are healing properly should not be considered ulceration. To warrant a positive response for ulceration, there should be evidence of a skin penetration that is often roundish and well-demarcated for which the participant can give no clear reason. They are sometimes painless and often occur over a pressure point or bony prominence at the heel, toe or metatarsal heads.

Question 3 records the findings of the ankle reflex test at the Achilles tendon and is answered by marking either Present, Present/Reinforcement (if the Jendrassic Maneuver was necessary to elicit the reflex), or Absent for each foot.

Question 4 records the results of the vibration perception tuning fork test of each foot. The answer is recorded by marking either Present, Reduced or Absent. A response of Present indicates that after the participant signaled that no more vibration of the tuning fork was felt, the tester could sense the vibration at the DIP of the index finger for only ≤10 seconds. A response of Reduced indicates that the vibration of the tuning fork at the DIP of the index finger was felt by the tester for >10 seconds, and a response of Absent indicates that the participant was unable to sense any vibration sensation of the tuning fork at the DIP of the great toe.

Question 5 records the number of monofilament applications detected at the dorsum of the great toe between the toe nail and the DIP joint. The answer is recorded by marking either Present, Reduced or Absent. A response of **present** indicates that the participant accurately detected >8 monofilament touches at the great toe. A response of **reduced** indicates the participant accurately detected 1-7 touches and a response of **absent** indicates the participant could not identify when the monofilament was being applied to the great toe.

Part C: MNSI Quality Control

A repeat MNSI examination (only the examination part of the test will be repeated) will be performed on approximately 5% of subjects at each site, by a separate examiner on the same day as the primary test. A random sample weighted towards younger participants with earlier estimated visit dates were selected for QC component.

The primary examiner (determined by the site) will perform the examination and record the results in the usual manner and enter the results into the SEARCH on-

line data entry program. The second examiner must not be present and must not see the results that the primary examiner has recorded.

The secondary examiner will perform the examination, record the results on a paper form, and place the results into a sealed envelope. This exam and recording is done outside the presence of the primary examiner. The primary and secondary examiner should not discuss their results until the primary test data has been entered and secondary test data has been entered. The CoC can then compare the QC and primary data for agreement. Sites will receive feedback regarding inter-examiner agreement. The CoC will to provide regular updates of primary/secondary tests to the University of Michigan. Disparities noted between examinations will be addressed with sites by Cathy Martin at the University of Michigan.

The subject identification on second form will need to indicate that the test is a quality control test - Write "QC" after the subject ID number. Also, both primary and secondary testers should be recorded.

K. Pediatric Diabetes Quality of Life Scale (PDQ) (2 versions: 10+ and parent)

Overview

Because diabetes is a complex chronic illness requiring constant self-monitoring, it is likely to have a significant impact on a participant or parent's daily living and quality of life. The PDQ will be used to evaluate and quantify the participant's quality of life as related to diabetes (a secondary outcome). Self-administration of this form should take approximately 5 minutes.

Questionnaire Administration

The 20 questions on the PDQ pertain to how much the prompt bothers the primary caregiver or the participant. For each of the 20 questions, the respondent should mark "1=A Lot," "2=Some," "3=Very Little," or "4=Not At All" in response to the question as to how much each prompt bothers him/her.

L. Quality of Life (PedsQL™ Administration Guidelines)

Overview

Diabetes is a complex chronic illness. Furthermore, both disease and treatment for the illness are likely to have significant impact on daily living and quality of life. Measuring and characterizing the impact of both on Health Related Quality of Life (HRQOL) are essential to understanding the broader impact of the illness.

As modern treatment advances improve mortality impact of chronic diseases, understanding the impact of the specific disease and its treatment on everyday

function and well-being has assumed greater importance. Thus, the HRQOL has emerged as an important outcome measure in clinical trials or observational studies.

Measuring HRQOL is especially important in diabetes where the treatment regimens such as eating restrictions or exercise requirements may have an impact on an individual's quality of life [16,19-21]. Thus, understanding how individuals appraise not only their overall quality of life, but also how they perceive their treatment regimens, are important. Participants may perceive their treatment as restrictive, negatively affecting their quality of life or in a more positive manner, likely leading to an enhanced overall quality of life. This will impact design of future interventions, improving adherence to regimen and ultimately impacting biologic measures [16,17,22-24].

Measurement Approach

The World Health Organization has defined health as a "State of complete physical, mental and social well-being and not merely the absence of diseases or infirmity" [25]. In this comprehensive framework, five aspects of health are outlined as the necessary components of an instrument for measuring HRQOL: physical health, mental health, social functioning, role functioning, and general health perceptions.

Two general approaches to measuring HRQOL have evolved: generic measures and disease specific measures [20,26]. Generic or non-specific assessments of HRQOL are usually multi-dimensional and broader in their scope [13,26-28]. They allow evaluation of different aspects of functioning applicable to participants across different illness groups. They are particularly useful for comparisons across illnesses, especially in determining utility as in cost-effectiveness comparisons of interventions across different conditions. For these same reasons, however, generic measures may be less sensitive to changes in function within individual illnesses. Disease-specific measures of HRQOL focus the assessment on narrower dimensions and specific problems associated with the illness or treatment. They may be more sensitive to measuring changes in HRQOL with clinical events or treatment regimens or even over time [10,12].

The Pediatric Quality of Life Inventory (PedsQL^{TM}) is a modular instrument designed to measure HRQOL in children and adolescents ages 2-18. The 23-item PedsQL 4.0 generic core scales are multidimensional child self-report and parent proxy report scales developed as the generic core measures to be integrated with the PedsQL disease-specific modules. The PedsQL diabetes module builds on this programmatic instrument development and measures three core areas with regard to diabetes HRQOL. The three areas include the symptom scale, the treatment

impact scale and the adherence scale. The generic PedsQL has been validated in large populations and has been shown to have internal consistency, reliability and the ability to distinguish between healthy children and pediatric participants with acute or chronic illness, and has also been shown to be related to indicators of morbidity or illness burden. The PedsQL diabetes module has been validated in adolescents with Type 1 or Type 2 Diabetes and has been shown to have internal consistency and validity. No data is currently available on test/retest validity or responsiveness to an intervention. In preliminary studies, the PedsQL diabetes module appears to differentiate between adolescents with Type 1 versus Type 2 diabetes.

Pediatric Quality of Life Inventory (PedsQL) questionnaires are broken down into 5 age groups: toddlers (2-4), young children (5-7), children (8-12), teens (13-18), and young adults (19 and older). Each age group has 2 sets of questions - one for generic measures and one for diabetes-specific measures. Parents will complete 2 sets of questions for all age groups (2-18) and participants who are 5 years of age or older will also complete 2 sets of questions.

M. Quality of Care Forms - Self Administered (2 versions)

Overview

The Institute of Medicine defines quality of health care as "the degree to which health services for individuals or populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [29]. This definition has provided the conceptual framework for advances in quality assessment in the last decade. SEARCH 3 continues and expands upon the measurement of quality of care initiated in SEARCH 1 and SEARCH 2 with emphasis on patient perceived quality and satisfaction with health care in general, and specifically for diabetes, conformity of care received to American Diabetes Association (ADA) guidelines for diabetes care for children and adolescents, measurement of clinical and qualitative outcomes of care, and self-care behaviors. SEARCH 2 explored the interrelationships of patient characteristics, important domains of health care with outcomes, including glycemic control, satisfaction with care, receipt of recommended services, complications, and quality of life.

Diversity in age, diabetes type and duration of diabetes has historically imposed significant limitations on studies of quality of care and quality of life for children and youth with diabetes. The SEARCH 3 Study, as a large scale, population-based study, designed to capture diversity in age, type and race/ethnicity, offers a unique opportunity to explore the complex relationships of patient characteristics, quality and outcomes of care.

SEARCH 3 expands the framework of quality of care to include Transition from Pediatric to Adult Care considerations. The forms are designed to be self-administered either in the clinic or at home. The participant version of the form is to be given ONLY to participants who are age 18 or over. If the participant is under age 18, the parent version of the form should be completed by the parent or guardian of the participant.

The participant version of the form consists of questions that refer to health care in general, including diabetes and non-diabetes care and providers. If the participant identifies differences among providers seen; they should be prompted to answer about their experiences in general, considering all of the care they have received.

The parent version consists of questions similar to the participant version. Questions on the parent version ask about transition from pediatric to adult care, diabetes self-care, hypoglycemia (within the last three months) eating, and blood sugar testing (within the last three months).

N. SphygmoCor Form (See section 15 of the MOP for specific details)

Instructions for completing the SphygmoCor can be found in Section 15 of the MOP (SphygmoCor). On the SEARCH SphygmoCor form, staff ask if caffeine, nicotine, and decongestants/asthma medications have been used on the morning of the SphygmoCor test. If a participant answers yes, record on the form what has been used. Continue with the test even if the participant has had caffeine, nicotine, decongestants, or asthma medication. Other information that is completed includes what the participant ate (if anything) prior to the test, the condition of the exam room (hot or cold), what measurements were obtained, all or partial measurements for Heart Rate Variability, Pulse Wave Velocity, and Pulse Wave Analysis for femoral, radial, and foot. There is also a space on the form for recording if the participant has been selected for a SphygmoCor QC measurement.

O. Supplemental Questionnaire (Age 10 & older)

Overview

The Supplemental Questionnaire is a self-administered form used to obtain the most accurate information from participants age 10 and older. Occasionally, children may not respond to perceived sensitive questions in the presence of parents or guardians. By asking similar questions to both the child and the parent/guardian, comparisons can be made to the validity of the response. Parents will be asked to waive their right to review answers to be provided by their children, with the assurance that appropriate referrals for care will be made according to established alert values for certain tests.

As SEARCH has progressed in its diversity of age population the staff has seen more alternative ways to addressing question number 13 on the questionnaire. As a means of clarifying the ways in which we document the self-reported information, if a participant writes in "tattoo" as a means of identification, staff are to consider it a "yes" response and code it as a bracelet when data entering the information.(12/2013)

Physical Activity

Physical inactivity has been identified as a key determinant of overweight and obesity in youth. Sedentary lifestyles in youth with diabetes may contribute to the constellation of cardiovascular disease risk factors that may occur with diabetes, particularly type 2 diabetes, including dyslipidemia and high blood pressure. Of particular interest in SEARCH, among non-diabetic youth, African American and Hispanic youth, as well as Asian males, are more likely to have inactive lifestyles than their non-Hispanic white counterparts [30,31].

Measurement Approach

To facilitate comparison with national survey data, questions on physical activity are taken from the CDC-sponsored Youth Risk Behavior Surveillance (YRBS)[31]. Similar to other brief approaches to physical activity assessment in youth, questions include frequency of vigorous and moderate activity, hours spent watching television, participation in physical education classes and participation in organized sports.

P. Tanner Stage Forms (Age 8 to 17 or until Stage 5 is reached)

Overview

Onset of puberty is associated with changes in insulin sensitivity and other metabolic and endocrine processes. Puberty is also associated with changes in social interactions and self-esteem. The Tanner Stage self-assessment of physical body changes will allow assessment of onset of puberty. Temporal sequence of puberty onset will help establish the relationship of puberty with insulin resistance and self-esteem, psycho-social factors, and/or depressive symptoms.

Administration of Form

The Tanner Stage Form is a self-administered form. **Different forms are supplied for males and females**.

Females

The participant should be given the form and informed to mark the box by each picture that most closely resembles their upper and lower body appearance. The participant should be given privacy while filling out this form.

Males

The participant should be given the form and informed to mark the box by the picture that most closely resembles their lower body appearance. The participant should be given privacy while filling out this form.

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APPENDIX A - REGISTRY LAB EXPLANATION

Diabetes antibodies - SEARCH measures 3 diabetes antibodies: GAD65, ZnT8 and IA2. Type 1 Diabetes occurs when the immune system destroys the insulin-producing cells of the pancreas. The diabetes antibodies are evidence of this process. The presence or absence of diabetes antibodies helps us to determine whether the individual has Type 1 Diabetes. Approximately 90% of people with Type 1 Diabetes have at least one of these antibodies present at the time of diagnosis.

C-peptide - measures how much insulin the pancreas is producing. The C-peptide level helps us to determine whether the individual has Type 1 Diabetes or Type 2 Diabetes. People with Type 1 Diabetes usually have low levels of C-peptide, while individuals with Type 2 Diabetes often have higher levels of c-peptide. C-peptide levels need to be measured while fasting because the results are affected by the amounts and types of food we eat.

Glucose - measures the sugar level in the blood. Glucose levels in the blood are usually higher in people with diabetes. SEARCH is measuring glucose levels to aid us in the interpretation of the c-peptide level.

Hemoglobin A1c - is a measure of the average blood sugar level over the past 3 months. Lower Hemoglobin A1c levels indicate "good" control, while higher levels indicate less control. SEARCH is measuring Hemoglobin A1c because higher levels may indicate that the individual is at increased risk for diabetes complications that affect the heart, eyes, kidneys, and nerves.

Lipid profile - measures the fat levels in the blood. It includes total cholesterol, triglycerides, LDL (the "bad" cholesterol), and HDL (the "good" cholesterol). It is best to have lower levels of total cholesterol, triglycerides, and LDL; and higher levels of HDL. SEARCH is measuring the lipid profile because high fat levels in the blood may indicate that the individual is at increased risk for diabetes complications related to the heart, such as a heart attack. Lipid profiles are most accurate when measured while fasting.

Urine albumin and creatinine - measures how much protein is being lost through the kidneys. SEARCH is measuring the protein level in the urine because high levels of protein may indicate that the individual is at increased risk for diabetes complications related to the kidney.

APPENDIX B - COHORT LAB EXPLANATION

Glucose - measures the sugar level in the blood. Glucose levels in the blood are usually higher in people with diabetes. SEARCH is measuring glucose levels to aid us in the interpretation of the c-peptide level.

Hemoglobin A1c - is a measure of the average blood sugar level over the past 3 months. Lower Hemoglobin A1c levels indicate "good" control, while higher levels indicate less control. SEARCH is measuring Hemoglobin A1c because higher levels may indicate that the individual is at increased risk for diabetes complications that affect the heart, eyes, kidneys, and nerves.

Lipid profile - measures the fat levels in the blood. It includes **total cholesterol**, **triglycerides**, **LDL** (the "bad" cholesterol), and **HDL** (the "good" cholesterol). It is best to have lower levels of total cholesterol, triglycerides, and LDL; and higher levels of HDL. SEARCH is measuring the lipid profile because high fat levels in the blood may indicate that the individual is at increased risk for diabetes complications related to the heart, such as a heart attack. Lipid profiles are most accurate when measured while fasting. **ApoB** and **DGUC Rf** are classifications of the LDL cholesterol; and higher levels of these may be associated with an increased risk for the development of heart disease.

Urine Albumin and Creatinine - Urine albumin and creatinine measures how much protein is being lost through the kidneys. SEARCH is measuring the protein level in the urine because high levels of protein may indicate that the individual is at increased risk for diabetes complications related to the kidney.

APPENDIX C - 90TH, 95TH AND 99TH +5 PERCENTILE BLOOD PRESSURES BY GENDER, AGE AND HEIGHT

			Pre Hypertension		High Blood Pressure		Seek Immediate Attention	
Gender	Age	Height	90th %ile	90th %ile	95th %ile	95th %ile	99th %ile+5	99th %ile+5
	(Years)	(Cm)	Systolic B/P	Diastolic B/P	Systolic B/P	Diastolic B/P	Systolic B/P	Diastolic B/P
Female	3	88	100	61	104	65	116	78
Female	3	89	100	62	104	66	116	78
Female	3	91	102	62	105	66	118	79
Female	3	94	103	63	107	67	119	79
Female	3	97	104	64	108	68	120	80
Female	3	99	106	64	109	68	121	81
Female	3	100	106	65	110	69	122	81
Female	4	94	101	64	105	68	117	81
Female	4	95	102	64	106	68	118	81
Female	4	98	103	65	107	69	119	81
Female	4	100	104	66	108	70	120	82
Female	4	103.5	106	67	110	71	122	83
Female	4	106	107	67	111	70	123	84
Female	4	108	108	68	112	71	124	84
Female	5	100	103	66	107	70	119	83
Female	5	102	103	67	107	71	119	83
Female	5	105	105	67	108	71	121	84
Female	5	107	106	68	110	72	122	84
Female	5	111	107	69	111	73	123	85
Female	5	114	109	69	112	73	125	86
Female	5	116	109	70	113	74	125	86
Female	6	106	104	68	108	72	120	85
Female	6	108	105	68	109	72	121	85
Female	6	111	106	69	110	73	122	85
Female	6	115	108	70	111	74	124	86
Female	6	118	109	70	113	74	125	87
Female	6	121.5	110	71	114	75	126	88
Female	6	124	111	72	115	76	127	88

Female	7	113	106	69	110	73	122	86
Female	7	115	107	70	111	74	123	86
Female	7	118	108	70	112	74	124	87
Female	7	121	109	71	113	75	125	87
Female	7	125	111	72	115	76	127	88
Female	7	129	112	72	116	76	128	89
Female	7	131	113	73	116	77	129	89
Female	8	118	108	71	112	75	124	87
Female	8	120	109	71	112	75	125	87
Female	8	124	110	71	114	75	126	88
Female	8	127	111	72	115	76	127	88
Female	8	132	113	73	116	77	128	89
Female	8	135	114	74	118	78	130	90
Female	8	135	114	74	118	78	130	91
Female	9	123	110	72	114	76	126	88
Female	9	125	110	72	114	76	126	88
Female	9	129	112	72	115	76	128	89
Female	9	133	113	73	117	77	129	89
Female	9	137	114	74	118	78	130	90
Female	9	141	116	75	119	79	132	91
Female	9	143	116	75	120	79	132	92
Female	10	127	112	73	116	77	128	89
Female	10	130	112	73	116	77	128	89
Female	10	133.5	114	73	117	77	130	90
Female	10	138	115	74	119	78	131	91
Female	10	143	116	75	120	79	132	91
Female	10	147	118	76	121	80	134	92
Female	10	150	118	76	122	80	134	93
Female	11	131	114	74	118	78	130	90
Female	11	135	114	74	118	78	130	90
Female	11	139	116	74	119	78	131	91
Female	11	144	117	75	121	79	133	92
Female	11	149	118	76	122	80	134	92
Female	11	153	119	77	123	81	135	93
Female	11	157	120	77	124	81	136	94

Female	12	138	116	75	119	79	132	91
Female	12	142	116	75	120	79	132	91
Female	12	146	117	75	121	79	133	92
Female	12	151	119	76	123	80	135	93
Female	12	156	120	77	124	81	136	93
Female	12	160	121	78	125	82	137	94
Female	12	164	122	78	126	82	138	95
Female	13	145	117	76	121	80	133	92
Female	13	148	118	76	122	80	134	92
Female	13	152	119	76	123	80	135	93
Female	13	157	121	77	124	81	137	94
Female	13	162	122	78	126	82	138	94
Female	13	166	123	79	127	83	139	95
Female	13	169	124	79	128	83	140	96
Female	14	149	119	77	123	81	135	93
Female	14	152	120	77	123	81	136	93
Female	14	156	121	77	125	81	137	94
Female	14	160	122	78	126	82	138	95
Female	14	165	124	79	127	83	140	95
Female	14	169	125	80	129	84	141	96
Female	14	172	125	80	129	84	141	97
Female	15	151	120	78	124	82	136	94
Female	15	154.5	121	78	125	82	137	94
Female	15	158.5	122	78	126	83	138	95
Female	15	162	123	79	127	83	139	96
Female	15	166	125	80	129	85	141	96
Female	15	170	126	81	130	85	142	97
Female	15	173	127	81	131	86	143	98
Female	16	152	121	78	125	82	137	95
Female	16	154	122	78	126	82	138	95
Female	16	158	123	79	127	83	139	95
Female	16	164	124	80	128	84	140	96
Female	16	167	126	81	130	85	142	97
Female	16	171	127	81	131	85	143	98
Female	16	174	128	82	132	86	144	98

Female	17	152	122	78	125	82	138	95
Female	17	155	122	79	126	83	138	95
Female	17	159	123	79	127	83	139	96
Female	17	163	125	80	129	84	141	96
Female	17	167	126	81	130	85	142	97
Female	17	171	127	81	131	85	143	98
Female	17	174	128	82	132	86	144	98
Female	>18				140	90	180	110

			Pre Hypertension		High Blood Pressure		Seek Immediate Attention	
Gender	Age	Height	90th %ile	90th %ile	95th %ile	95th %ile	99th %ile+5	99th %ile+5
	(Years)	(Cm)	Systolic B/P	Diastolic B/P	Systolic B/P	Diastolic B/P	Systolic B/P	Diastolic B/P
Male	3	89	100	59	104	63	116	76
Male	3	90	101	59	105	63	117	76
Male	3	93	103	60	107	64	119	77
Male	3	95	105	61	109	65	121	78
Male	3	97.5	107	62	110	66	123	79
Male	3	100	108	63	112	67	124	80
Male	3	102	109	63	113	67	125	80
Male	4	96	102	62	106	66	118	79
Male	4	97	103	63	107	67	119	80
Male	4	100	105	64	109	68	121	81
Male	4	103	107	65	111	69	123	82
Male	4	106	109	66	112	70	125	83
Male	4	108	110	66	114	71	126	83
Male	4	110	111	67	115	71	127	84
Male	5	102	104	65	108	69	120	82
Male	5	104	105	66	109	70	121	83
Male	5	107	106	67	110	71	123	84
Male	5	110	108	68	112	72	125	85
Male	5	113	110	69	114	73	126	86
Male	5	115	111	69	115	74	128	86
Male	5	117	112	70	116	74	128	87

Male	6	108	105	68	109	72	121	82
Male	6	110	106	68	110	72	122	83
Male	6	112.5	108	69	112	73	123	84
Male	6	116	110	70	114	74	125	85
Male	6	119	111	71	115	75	126	86
Male	6	122	113	72	117	76	128	86
Male	6	123	113	72	117	76	128	87
Male	7	113	106	70	110	74	122	87
Male	7	115	107	70	111	74	123	87
Male	7	118	109	71	113	75	125	88
Male	7	122	111	72	115	76	127	89
Male	7	125	113	73	117	77	129	90
Male	7	128	114	74	118	78	130	91
Male	7	130	115	74	119	78	131	91
Male	8	118	107	71	111	75	124	88
Male	8	120	109	72	112	76	125	89
Male	8	123	110	72	114	77	127	90
Male	8	127	112	73	116	78	128	91
Male	8	130	114	74	118	79	130	92
Male	8	133	115	75	119	79	132	92
Male	8	135	116	76	120	80	132	93
Male	9	123	109	72	113	76	125	89
Male	9	125	110	73	114	77	126	90
Male	9	128	112	74	116	78	128	91
Male	9	132	114	75	118	79	130	92
Male	9	136	115	76	119	80	132	93
Male	9	139	117	76	121	81	133	93
Male	9	141.5	118	77	121	81	134	94
Male	10	128	111	73	115	77	127	90
Male	10	130	112	73	115	78	128	91
Male	10	133	114	74	117	79	130	91
Male	10	137	115	75	119	80	132	93
Male	10	141	117	76	121	81	133	93
Male	10	145	119	77	122	81	135	94
Male	10	147	119	78	123	82	135	95

Male	11	132	113	74	117	78	129	91
Male	11	135	114	74	118	78	130	91
Male	11	138	115	75	119	79	132	92
Male	11	143	117	76	121	80	134	93
Male	11	147	119	77	123	81	135	94
Male	11	152	120	78	124	82	137	95
Male	11	154.5	121	78	125	82	137	95
Male	12	137	115	74	119	78	131	91
Male	12	140	116	75	120	79	132	92
Male	12	144	118	75	122	80	134	93
Male	12	149	120	76	123	81	136	94
Male	12	154	121	77	125	82	138	95
Male	12	159	123	78	127	82	139	95
Male	12	162	123	79	127	83	140	96
Male	13	142.5	117	75	121	79	133	92
Male	13	145	118	75	122	70	135	92
Male	13	150	120	76	124	80	136	93
Male	13	156	122	77	126	81	138	94
Male	13	161	124	78	128	82	140	95
Male	13	166	125	79	129	83	141	96
Male	13	169	126	79	130	83	142	96
Male	14	148	120	75	124	80	136	92
Male	14	151	121	76	125	80	137	93
Male	14	156	123	77	127	81	139	94
Male	14	163	125	78	128	82	141	95
Male	14	168	126	79	130	83	143	96
Male	14	173	128	79	132	84	144	97
Male	14	176	128	80	132	84	145	97
Male	15	155	122	76	126	81	139	93
Male	15	158	124	77	127	81	140	94
Male	15	163	125	78	129	82	141	95
Male	15	169	127	79	131	83	143	96
Male	15	174	129	80	133	84	145	97
Male	15	178.5	130	80	134	85	147	98
Male	15	181.5	131	81	135	85	147	98

Male	16	161	125	78	129	82	141	95
Male	16	163.5	126	78	130	83	142	95
Male	16	168	128	79	132	83	144	96
Male	16	173	130	80	134	84	146	97
Male	16	178	131	81	135	85	148	98
Male	16	182	133	82	137	86	149	99
Male	16	185	134	82	137	87	150	99
Male	17	165	127	80	131	84	144	97
Male	17	167.5	128	80	132	85	145	98
Male	17	172	130	81	134	86	146	98
Male	17	176	132	82	136	87	148	99
Male	17	180	134	83	138	87	150	100
Male	17	184	135	84	139	88	151	101
Male	17	187	136	84	140	89	152	102
Male	>18				140	80	180	110

APPENDIX D - SECONDARY DIABETES IDENTIFIED DURING OR AFTER AN IN-PERSON VISIT

NOT Valid
No Diabetes Diagnosed
Glucose Intol.:
Glucose Intol.: Fasting - Normal/High Insulin
Glucose Intol.: Fasting - Low Insulin
Glucose Intol.: Fasting - Insulin Unknown
Glucose Intol.: Post Prandial - Normal/High Insulin
Glucose Intol.: Post Prandial - Low Insulin
Glucose Intol.: Post Prandial - Insulin Unknown
Glucose Intol.: Fasting & Post-Prandial - Norm/High
Glucose Intol.: Fasting & Post-Prandial - Low Ins.
Glucose Intol.: Fasting & Post-Prand. - Ins Unknown
Glucose Intol.: Unknown
Insulin Resistance
Stress Hyperglycemia
Gestational diabetes mellitus (GDM)

Valid
Fully Eligible - for In-Person Visit
Type 1 Diabetes:
Type 1 Diabetes: Immune mediated
Type 1 Diabetes: Idiopathic
Type 1 Diabetes: Unknown
Type 2 Diabetes
Unclassified
Genetic Defect B-cell:
Genetic Defect B-cell: Chrom. 12, HNF-1a(MODY3)
Genetic Defect B-cell: Chrom. 20, HNF-4a(MODY1)
Genetic Defect B-cell: Chrom. 7 glucokinase(MODY2)
Genetic Defect B-cell: Mitochondrial DNA
Genetic Defect B-cell: Others

Secondary - complete IPS only
Dis. Exocrine Pancreas:
Dis. Exocrine Pancreas: Cystic Fibrosis
Dis. Exocrine Pancreas: Neoplasia
Dis. Exocrine Pancreas: Fibrocalcul Pancreatopathy
Dis. Exocrine Pancreas: Hemochromatosis
Dis. Exocrine Pancreas: Pancreatitis
Dis. Exocrine Pancreas: Trauma/Pancreatectomy
Dis. Exocrine Pancreas: Others
Drug or chemical induced:
Drug or chemical induced: Glucocorticoids
Drug or chemical induced: B-adrenergic agonists
Drug or chemical induced: Diazoxide
Drug or chemical induced: Dilantin
Drug or chemical induced: Nicotinic Acid
Drug or chemical induced: Pentamidine
Drug or chemical induced: Thiazides
Drug or chemical induced: Thyroid Hormone
Drug or chemical induced: Vacor
Drug or chemical induced: a-interferon
Drug or chemical induced: Others
Endocrinopathies:
Endocrinopathies: Acromegaly
Endocrinopathies: Aldosteronoma
Endocrinopathies: Cushing's syndrome
Endocrinopathies: Glucagonoma
Endocrinopathies: Hyperthyroidism
Endocrinopathies: Pheochromocytoma
Endocrinopathies: Somatostatinoma
Endocrinopathies: Others
Genetic Defect Ins. action:
Genetic Defect Ins. action: Lephrechaunism
Genetic Defect Ins. action: Lipoatrophic diabetes
Genetic Defect Ins. action: Rabson-Mendenhall syn.

Genetic Defect Ins. action: Type A ins. resist.
Genetic Defect Ins. action: Others
Infections:
Infections: Congenital rubella
Infections: Cytomegalovirous
Infections: Others
Other genetic syn.:
Other genetic syn.: Down's syndrome
Other genetic syn.: Friedreich's ataxia
Other genetic syn.: Huntington's chorea
Other genetic syn.: Klinefelter's syndrome
Other genetic syn.: Laurence-Moon-Biedl syn.
Other genetic syn.: Myotonic dystrophy
Other genetic syn.: Porphyria
Other genetic syn.: Prader-Willi syndrome
Other genetic syn.: Turner's syndrome
Other genetic syn.: Wolfram's syndrome
Other genetic syn.: Others
Uncommon Immune Types:
Uncommon Immune Types: "Stiff-man" syndromes
Uncommon Immune Types: Anti-ins receptor antibody
Uncommon Immune Types: Others
Neonatal