SEARCH MOP - Section 17
Patient Safety, Alert Values, Event Reporting & Monitoring
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17. Patient Safety, Alert Values, Event Reporting and Monitoring

17.1. OVERVIEW

Blood glucose fluctuation is inherent in diabetes. Dietary intake and medication administration may affect patients' blood glucose levels and the occurrence of various signs and symptoms, such as nausea, abdominal pain, ketosis, and level of consciousness. SEARCH participation could affect blood glucose levels because SEARCH study procedures involve the temporary modification of diet and medication usage. The fact that patients in SEARCH may experience the same high and low blood glucose levels and symptoms both as an inherent part of their disease and as a result of study procedures complicates the determination of study relatedness.

In both the Registry and Cohort Studies lab specimen collections will be taken. Procedures in each study have been outlined to assure the safety of SEARCH participants. These sections describe the plan for the prevention and monitoring of alert values and events that are expected to occur in a small percentage of SEARCH participants.

17.2. DEFINITIONS

17.2.1. *Anticipated Occurrences and Alert Values*

Anticipated occurrences and alert values are conditions that are expected to occur in a subset of participants and require some type of response by study personnel. For this study, fainting due to phlebotomy is considered an anticipated occurrence. In addition, alert values have been identified for glucose levels, blood pressure, triglyceride levels, and CES-D scores. See Table 17.1 for more details. Fainting due to phlebotomy is "definitely related" to study procedures, while alert values may or may not be related to study procedures.

17.2.2. *Unanticipated Occurrences*

Unanticipated occurrences are conditions or events that are NOT expected to occur within the normal course of study participation.

17.2.3. *Study Relatedness*

<u>Definitely Related</u>

An occurrence that has a timely relationship to the administration of the study procedure and follows a known pattern of response for which no alternative cause is present (e.g., a SEARCH study patient faints while blood is being drawn).

<u>Probably Related</u>

An event that has a timely relationship to the administration of the study procedure and follows a known pattern of response, but for which a potential alternative cause may be

present (e.g., a SEARCH patient with normally good glucose control has a fasting glucose of >300 mg/dl, with or without ketones, after withholding their usual morning dose of insulin).

Possibly Related

An event that has a timely relationship to the study procedure and follows no known pattern of response, but a potential alternative cause does not exist (e.g., a SEARCH patient has an infection, such as a "strep throat" or a "cold," and has a fasting glucose level of >300 mg/dl, with or without ketones).

Unrelated

An event for which there is evidence that it is definitely related to a cause other than the procedure; in general, no timely relationship to the study procedure exists, or if so, the event does not follow a pattern of response and an alternative cause is present (e.g., a child with a seizure disorder has a seizure during the SEARCH study exam even though they took their seizure medication on schedule).

17.3. PATIENT SAFETY

17.3.1. *Overview*

Each SEARCH site will have guidelines for handling anticipated occurrences (fainting due to phlebotomy) and alert values (e.g., hyperglycemia or elevated blood pressure) that are expected to occur in a small percentage of SEARCH participants. Guidelines for potential staff responses to these occurrences and alert values are also outlined. These guidelines are site-specific, reflecting the care setting in which the study is being conducted, differences in the availability and training of site personnel, and differences in the relationship of study personnel to the SEARCH patient. Sites will also include guidelines for handling seizures and/or loss of consciousness due to hypoglycemia.

Table 17.1 lists conditions and alert values that must be included in site-specific guidelines to assure patient safety along with some of the potential actions to manage these situations.

Table 17.1. Guidelines for Patient Safety

Condition/Alert Value	Actions
Glucose Level	
▪ Less than 45 mg/dl	Intervene prior to obtaining SEARCH laboratory specimens With no symptoms or mild symptoms, administer 4 oz. juice if patient is able to take fluids; recheck glucose level within 15 minutes

Condition/Alert Value	Actions
	*With loss of consciousness or seizure, administer intravenous glucose (3 cc/kg of 10% dextrose) OR glucagon (0.3 - 1 mg intramuscular injection) OR glucose gel **AND CALL 911***
	Be certain that patient has eaten and glucose has been rechecked prior to his/her departing from the study site
▪ Greater than 300 mg/dl	Check for the presence of urinary ketones, physical signs (nausea, vomiting, and abdominal pain). If ketones and/or symptoms present, obtain medical assessment from qualified medical personnel
	If patient takes insulin, obtain assistance in recommending insulin dose adjustment from qualified medical personnel and arrange for follow-up; encourage intake of sugar-free fluids
▪ Greater than 500 mg/dl	Obtain medical assessment from qualified medical personnel either on-site or in an emergency or urgent care facility
Phlebotomy	
▪ Fainting ▪ Lightheadedness, dizziness ▪ Nausea at the time of phlebotomy	Check blood sugar level. If blood sugar is low, implement actions to raise glucose level (see above). Have the patient lie down, apply a cold compress to forehead, and offer water to drink. Stay with the patient until symptoms have resolved. If symptoms do not resolve, obtain medical assessment from qualified on-site personnel
Seizure /Loss of Consciousness	
Seizure /Loss of Consciousness	If seizure or loss of consciousness occurs due to hypoglycemia:
	Administer glucose gel OR glucagon (0.3 - 1 mg intramuscular injection) OR intravenous glucose (3 cc/kg of 10% dextrose) **AND CALL 911**
High CES-D score	
Both Males and Females:	
< 18 yrs. of age: ≥ 24 for subjects	Inform parent/patient of finding Query if under treatment
18 yrs. of age or older: ≥ 16 for subjects.	Identify source for follow-up care if not under treatment

Condition/Alert Value	Actions
Blood Pressure	
3 yrs to 17 yrs	95thile - High Blood Pressure
	99thile+5 - Seek immediate medical attention
18 yrs. of age or older	
140/90	High Blood Pressure
>180/110	Refer the patient to their care provider or the Emergency Room for immediate attention
Severe Hypertriglyceridemia	
>1000 mg / dl	Central laboratory to notify PI or his/her designee within 24 hours. Contact patient's care provider

17.3.1.1. Urine Samples

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.

The participant is informed of blood in the urine if both the first morning void and the random urine are positive (moderate to large) for blood with the recommendation that the participant contact their provider/primary care physician for further evaluation. The method of contact by the SEARCH Clinical center (letter, phone call) will be performed as per local guidelines. (2/13)

17.3.1.2. Neuropathy Evaluation (MNSI)

Section 16 (MNSI) outlines all the details of the neuropathy evaluation. During an in-person SEARCH visit, if an untreated ulcer or infection is found during inspection of the feet by the research staff, the research team member will recommend that the participant contact their provider/primary care physician for evaluation and treatment. The research staff will document in the research chart the findings and recommendation. (2/13)

17.3.1.3. Retinal Photo Reports

SEARCH pathology notification will be generated after images have been reviewed by the Reading Center and an abnormality has been detected. A form will be faxed to the Coordinating Center and the site coordinator when significant pathology is noted. Normally this will be within 2 to 3 days of receipt of the images from the site. Occasionally an abnormal condition may go undetected at the first screening and the notification will not occur until a more detailed review is completed. Pathology notifications will be either **immediate** or **early**. An **immediate** notification indicates the participant should be seen by his or her eye care provider (ophthalmologist or optometrist) as soon as possible. An **early** notification indicates the participant should be seen by an eye care provider within two months. Persons who receive an early notification either have conditions that may be slowly progressive or considered less likely to affect vision over a short period of time. Because the Reading Center usually has little historical or examination information regarding the participant's past history or current eye care, it is possible that the participant is aware of the condition and is under the care of an ophthalmologist or optometrist for it. **If an immediate or early notification is sent by the Reading Center, the clinical site will notify the participant and/or provider according to local guidelines. The urgency of this notification will be based on category assigned by the Reading Center.** (2/13)

17.3.1.4. SphygmoCor

If the participant experiences or spontaneously reports symptoms (dizziness, lightheadedness, shortness of breath, fainting) during the research visit, the research team member will contact the PI or clinically trained designee at the clinical site for recommendations regarding immediate action (send the participant to ER or refer to participant's family physician. The blood pressure alerts already used by SEARCH and described above will be used for the guidelines. If the research team member notes a concern on the SphygmoCor tracing and the participant is not experiencing or spontaneously reporting any symptoms (dizziness, lightheadedness, shortness of breath, fainting), the research team member will save a screen shot and send the screen shot by email to Elaine Urbina for review and interpretation. Further action will be dictated by Elaine's interpretation. See detailed instructions in Section 15 SphygmoCor MOP page 54. (2/13)

17.4. PREVENTION OF STUDY-RELATED HYPERGLYCEMIA AND HYPOGLYCEMIA

Patients, families and providers may have multiple methods for preventing hypoglycemia and hyperglycemia related to study procedures. All sites should try to minimize the duration of time a fasting patient must wait before laboratory specimens can be drawn and nutrition provided and insulin or oral medication administered. The following are examples of

approaches that may help minimize the impact of SEARCH procedures on the participant's blood glucose level. These are not the only approaches to accomplish the aim of preventing hypoglycemia and hyperglycemia related to study participation. Sites should develop processes that reflect the local situation, and reflect the relationship between study personnel and the patient.

One approach to preventing high glucose at the time of the fasting in-person visit that can be used when the site PI is also the patient's managing physician is modification of the dose of NPH insulin taken the evening prior to the visit. If the AM appointment is later than 9:00 AM, the patient/parent can be instructed to split the evening dose of insulin, administering the usual PM dose of fast-acting insulin (Regular or Humalog) prior to supper and administering 80% of the usual dose of NPH insulin at 10:00 PM. The split-dose method of insulin administration in the evening is a standard of care for patients who rise late in the AM and prolongs the coverage of insulin in the AM. This method of split-dose insulin does not increase the risk of nocturnal hypoglycemia.

Hypoglycemic may occur when the patient's average morning blood glucose is less than 150 mg/dl *or* 3 of 7 fasting blood glucose were less than 100 mg/dl during the past week. The risk of hypoglycemia in this circumstance might be prevented by decreasing the evening NPH insulin dose by 10 to 20% the evening prior to the study visit. This could be attempted when the site PI is also the patient's managing physician.

One method of preventing hypoglycemia when a patient has administered their insulin and refused food is to not release the patient from the clinic until they have eaten food or consumed fluids containing glucose. Another method of preventing both hypoglycemia and hyperglycemia is to schedule the patient for a split visit schedule. This method would allow the interview and physical examination, which do not require the patient be fasting or modify their medication, to be done at one visit and laboratory specimens at a separate visit. When this method is utilized, fasting specimens should be drawn as soon as possible to avoid difficulty. Once the fasting laboratory specimens are obtained, food and medication should be given immediately. Consent for obtaining blood specimens can be obtained at the first visit to further reduce the time between arrival and food intake.

17.5. ANTICIPATED OCCURRENCES AND ALERT VALUES

Anticipated occurrences (fainting due to phlebotomy) and alert values (e.g., hyperglycemia or elevated blood pressure) are expected to occur in a small percentage of SEARCH participants. When these conditions are identified, study personnel should implement response actions identified by local guidelines. Because these occurrences and alert values are anticipated, they do NOT need to be reported on the Unanticipated Occurrence/Condition Reporting Form.

17.6. UNANTICIPATED OCCURRENCES

Unanticipated occurrences or conditions are NOT expected to occur within the normal course of study participation. These occurrences DO need to be reported on the Unanticipated Occurrence/Condition Reporting Form.

17.7. UNANTICIPATED OCCURRENCE/CONDITION REPORTING FORM.

17.7.1. *Reporting*

The following occurrences or conditions will be reported to the CoC via the SEARCH Unanticipated Occurrence/Condition Reporting Form:

- Loss of consciousness due to low blood glucose
- Seizure
- Any other untoward event that is NOT anticipated and related to study procedures

17.7.1.1. SEARCH Unanticipated Occurrence/Condition Reporting Form

- Enter the date of the event in the area provided - MM DD YYYY
- Check the appropriate visit type – *Registry visit, Cohort visit* or *other*. If "other" please specify the type of visit.

Description of Unanticipated Occurrence/Condition

Question 1 asks for a description of the occurrence or condition. Select one or more of the following: loss of consciousness due to low blood glucose, seizure, or other (e.g., injury resulting from a fall at the study site). The "other" category allows for a description of the event.

Question 2 asks if any actions were implemented.

Check any actions that may have been taken. If "other" is checked, please specify in box provided.

Event Severity and Relationship

Question 3 asks if the event is a serious adverse event**.**

A serious adverse event is defined as any event that results in hospitalization, disability, or death. Serious adverse events should be reported to the CoC and the local IRB within 24 hours.

Question 4 asks the relationship of the event to study procedures or treatment.

See Section 17.2.2. for definitions of *definitely, probably, possibly* or *unrelated* to the study.

Question 5 asks for a comment regarding the circumstances of the event and any follow-up measures that may have been implemented.

17.7.2. *Monitoring and Review*

The CoC will prepare quarterly reports. These reports will be reviewed by an external safety monitor and members of the POC committee. The external monitor may make recommendations for modifications of study procedures based on his/her independent review of study events.

17.7.2.1. External Monitor Safety Reports

The external monitor will provide interim and annual reports to the Director of the CoC and the POC committee. The interim reports will be quarterly and will summarize unanticipated events that are related to study procedures. These interim reports will be reviewed by the POC committee, allowing for discussion among the external monitor and POC committee members. The annual report will summarize the findings of the monitor over the previous calendar year. Monitor reports will be written on academic letterhead, dated, and signed by the monitor. They will describe any unanticipated events and will include comments about types of events, relatedness to the study, event rates, and any other issues related to study safety. These reports will be submitted to the principal investigators.