T TRIAL CARDIOVASCULAR ASSESSMENT
MANUAL OF PROCEDURES
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1 INTRODUCTION

An important goal of the T Trial is to determine if testosterone treatment is associated with cardiovascular adverse events. The trial will approach this goal in two ways:

- participant self-report of cardiovascular symptoms
- hospitalization record/chart abstraction to determine whether a cardiovascular event occurred, the type of event and the degree of certainty regarding its occurrence (for example, definite versus probable)

This document describes the activities that identify, document, and classify the occurrence of study-related cardiovascular events.

1.A STUDY EVENTS

During the T Trial, investigators will track the cardiovascular events of all participants. All events will require investigation. An Events Adjudication Committee of specialists in cardiology and neurology will be established to adjudicate myocardial infarction (MI) and stroke and verify other cardiovascular events. The events of interest are listed below.

- Cardiac Events
  - Myocardial infarction (MI)
  - Angina
  - Congestive heart failure (CHF)
  - Coronary revascularization due to symptoms
- Cerebrovascular Events
  - Stroke
- Peripheral Vascular Events
- Cardiovascular Deaths

2 OVERVIEW OF ASSESSMENT PROCESS

2.A Cardiovascular History

At the baseline visit, the RC will complete the Cardiovascular-Metabolic History (CVHX) form with the participant. This form provides specific information about:

- Cardiac history
- Cerebrovascular history
- Peripheral vascular history
- Hypertension history
- High cholesterol history
- Diabetic history
- Smoking history
- Chronic lung disease history

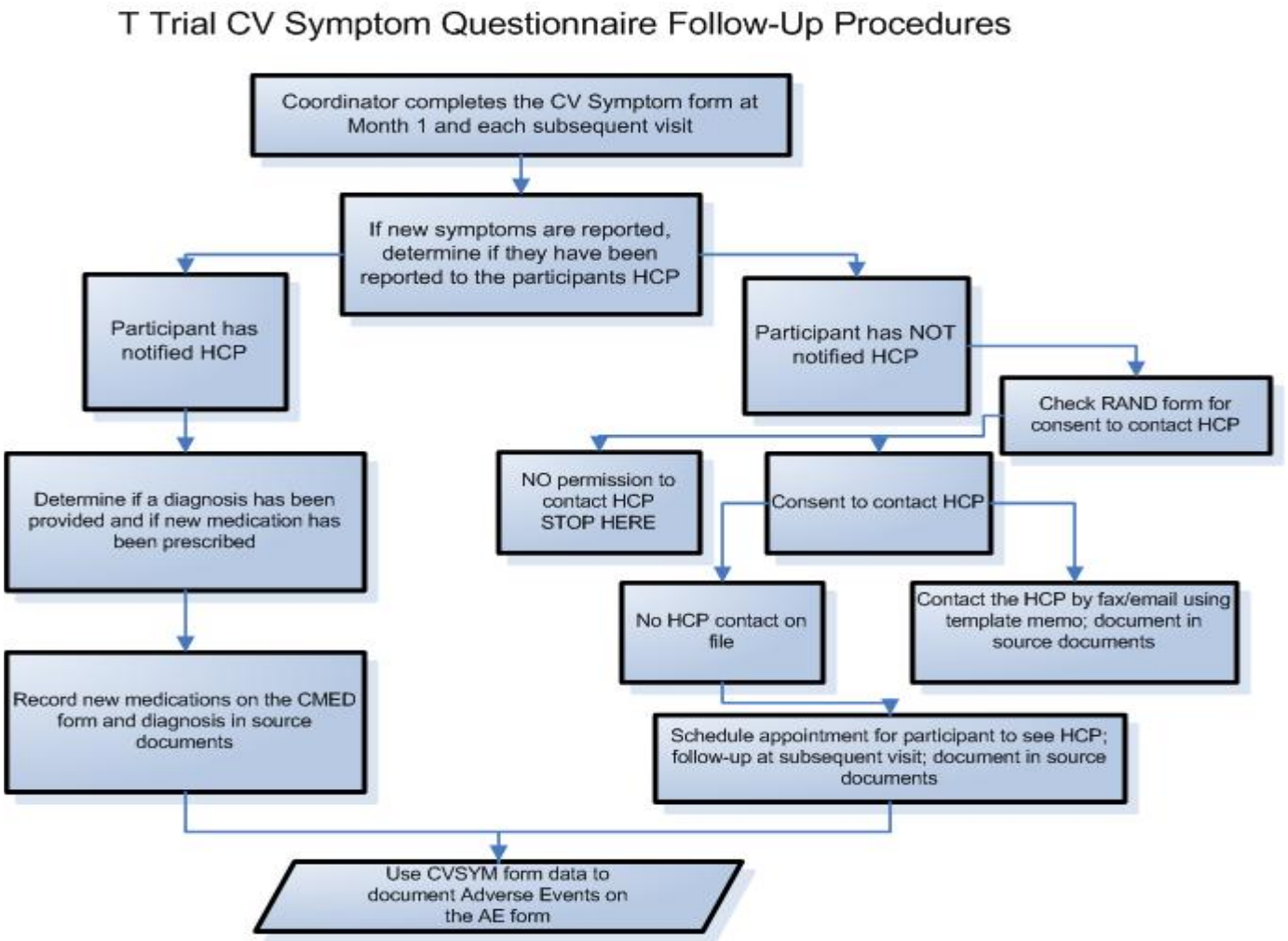
This information will characterize each participant in terms of his history and pre-existing conditions and will serve as a reference point for monitoring the occurrence of new or worsening of pre-existing cardiovascular events and conditions.

2.B Cardiovascular Symptoms

During each in-person T Trial visit, beginning at the Month 1 visit, participants will be asked to complete the CV Symptom Questionnaire (CVSYM) as an interview with the RC. The components of this form are focused on:

- Cerebrovascular symptoms (TIA and stroke)
- Cardiac symptoms (angina and CHF)
- Peripheral vascular disease
- Other important symptoms

This form will be entered into the Data Management System and will serve as a basis for reporting adverse events. Each new symptom must also be transcribed to the Adverse Event (AE) form. The RC will have a discussion with the participant to determine if the new symptom(s) has/have been reported to the participant's Health Care Provider (HCP). If it has, then the RC will document that information in the source document and follow-up on changes in symptoms at subsequent visits. If, however, a participant reports that he has not reported new symptoms to his HCP, the RC must take steps to ensure that this information is communicated to the HCP. If a participant does not have a HCP, the RC must arrange for referral and an appointment. This information should be communicated to the HCP within 2 to 3 days. The diagram below provides an overview of the symptom assessment process:



2.C Cardiovascular Events

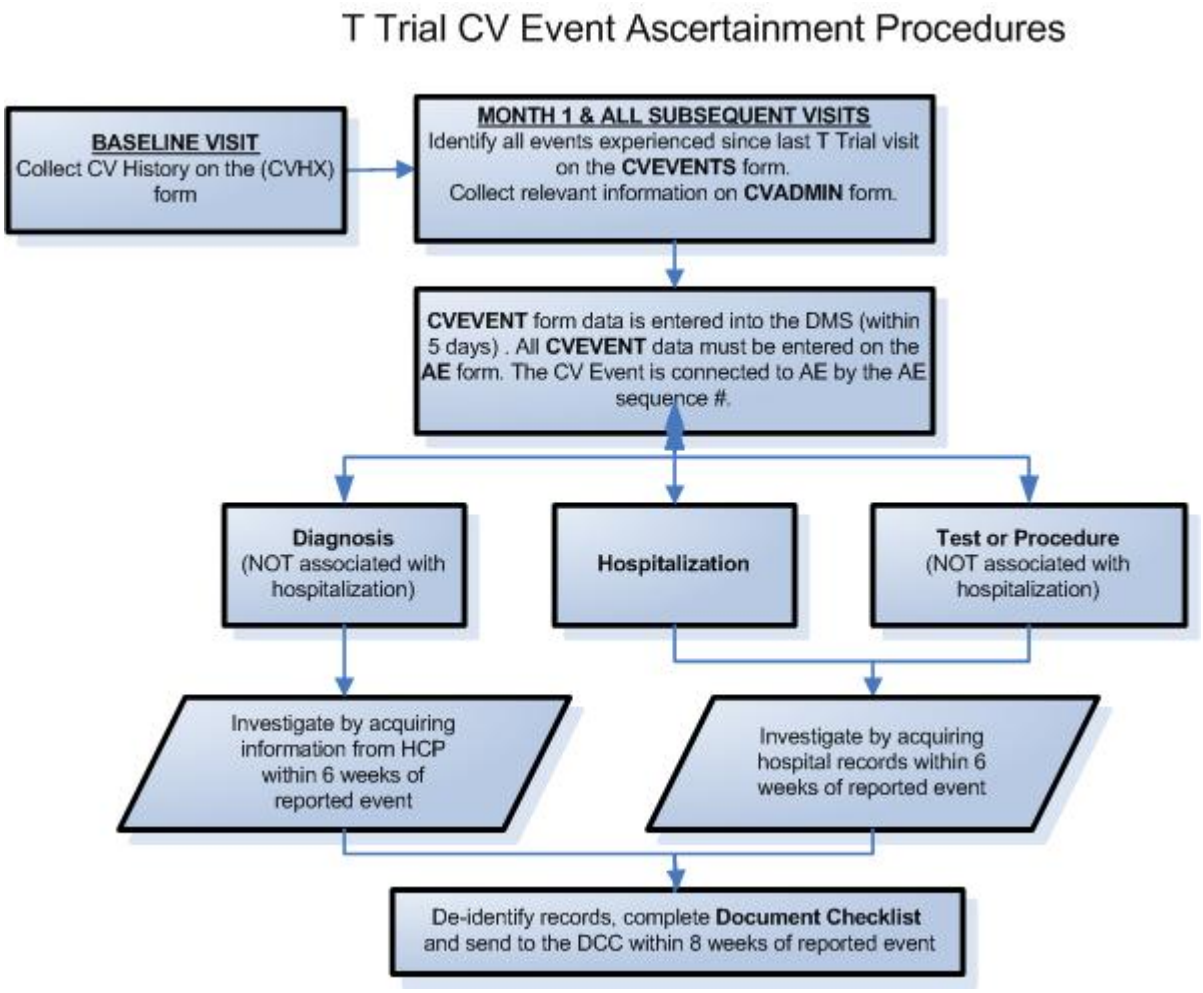
The events ascertainment process will identify, track, investigate, and determine if a study-related event has occurred. At each in-person visit after the baseline visit, a participant will be asked if he has experienced any of the defined events since his last visit. This information is collected on the CVEVENTS form and entered into the T Trial Data Management System (DMS). All information from this form is also recorded on the AE form. The corresponding AE sequence number will be used to track the event investigation.

2.C.1 Identifying Events

The following events will require investigation:

1. A diagnosis of MI, stroke, atrial fibrillation, vascular disease of the legs, angina or heart failure **NOT** associated with a hospitalization but reported to the participant by his health care provider (See section 1 of the CVEVENTS form.)
    - Events in this category will require follow-up with the participant's health care provider.
2. Hospitalization or Emergency department visit for MI, angina, heart failure, cardiac surgery, arrhythmia, stroke, carotid artery disease, peripheral arterial disease, deep vein thrombosis (See section 2 of the CVEVENTS form.)
    - Events in this category will require acquisition of medical records for the hospitalization or ED visit.
    - IMPORTANT NOTE: Events in this category are Serious Adverse Event (SAE), and will require documentation on the MedWatch form.
    - IMPORTANT NOTE: Events in this category must be reported to the DCC within 24 hours of first knowledge of the event.
3. Outpatient procedures: echocardiogram, cardiac stress test, head CT or MRI for condition other than sinus problem, Holter monitor (See section 3 of the CVEVENTS form.)
    - Events in this category will require acquisition of medical records for the outpatient procedure. Procedures that occur during a hospitalization are investigated as part of the hospitalization record.

The figure below provides an overview of the event ascertainment process:



3 PROCESS RESPONSIBILITY

The investigation of possible events depends on the careful collection and review of information from multiple sources. It also relies on the active collaboration and communication of clinical sites, the DCC, and the Events Adjudication Committee. While their efforts contribute to the common goal of tracking participant events over the duration of the study, these groups have separate and discrete responsibilities which are described in detail in the following sections.

3.A Clinical Site Responsibilities

Throughout the ascertainment process, clinical site personnel are actively involved in a variety of tasks that principally include screening for events and collecting accurate and comprehensive information. Clinical site personnel are responsible for:

- Maintaining up-to-date medical record release and HIPAA authorization forms for each participant according to each institution's guidelines
- Administering the CVSYM and CVEVENTS questionnaires to T Trial participants at each in-person visit and entering forms into the DMS within 5 days
- Communicating with participant HCP about newly reported symptoms if the participant has not done so within 2 to 3 days
- Referring participants to a HCP for evaluation of reported new symptoms if the

participant has not identified a HCP
- Completing the CVADMIN form to acquire medical records.
- Performing an event investigation. For each hospitalization, site personnel should:
  - Obtain consent from the participant to acquire medical records if not already done or if consent has expired.
  - Request/obtain relevant medical records within 6 weeks of the reported event
  - Complete the Document Checklist (DOCLIST) for each event
- Copy and de-identify medical records.
- Compile de-identified records and supporting documentation for each event and send to the DCC within 8 weeks of the reported event.

3.B DCC Responsibilities

The DCC plays an integral role in coordinating and managing the flow of event information and documentation between the clinical sites and the Events Adjudication Committee. Its primary functions are to:

- Provide clinical sites with help and support for event investigations, via conference calls and regular phone/email contacts initiated by the sites.
- Receive, review, track, and archive all of the medical records and supporting documentation submitted by the clinical sites for each event investigation.
- Track event investigation process until complete for each case. Prompt clinical sites when forms are overdue.
- Prepare and transmit the medical records and supporting documentation to physician reviewers in the Event Adjudication Committee.
- Enter final review CRFs into the DMS when they are returned by the physician reviewers.
- Generate a report of events for review by the DSMB.

3.C Event Adjudication Committee Responsibilities

The Event Adjudication Committee is composed of physician reviewers in the specialties of cardiology and neurology. Committee members are responsible to:

- Review medical records and supporting documentation for all event investigations
- Complete and submit case report forms required for event determination
- Determine whether investigated events meet specified definitions

4 CV FORMS AND DATA COLLECTION PROCEDURES

This section provides specific instructions on how to complete the symptom and event case report forms. If, after reading this section, you are still unsure about case report form completion, contact the T Trial Project Management Team.

4.A *Cardiovascular-Metabolic History* [CVHX]

Purpose: This form focuses on specific symptoms and diagnoses related to cardiovascular disease and related aspects of medical history.

Who: This form should be completed by the RC via an interview with the participant.

When: This history is completed at the baseline visit only.

Directions: Begin by setting the time frame for the participant. This form asks if the participant has **ever** been told that he had the listed conditions.

- All questions must be answered.
- If a participant does not remember at what age he received a diagnosis or started taking medication, ask him to make his best estimate.

Q. 8. There is a skip pattern if a participant has never been told that he has high blood pressure.

Q. 9. There is a skip pattern if a participant has never been told that he has high cholesterol.

Q.10. There is a skip pattern if a participant has never been told that he has diabetes.

Q.14. There is a skip pattern if a participant has not smoked 100 cigarettes. There is an internal skip pattern if a participant is not a current smoker. The purpose of these questions is to determine if a person is a current smoker, former smoker or has never smoked.

- Record concomitant medications reported during the administration of this form on the CMED form.

4.B *CV Symptom Questionnaire* [CVSYM]

In completing the symptom questionnaire, the RC should use his/her best clinical judgment in assessing participant's reported symptoms and events. The symptom assessment should be completed before the adverse event (AE) form.

Purpose: This survey focuses on symptoms related to cardiac and cerebrovascular events. The RC completing the form must verify that the participant has informed his HCP about the reported symptoms. This information should be written in the source document.

Who: This symptom survey should be completed by the RC via an interview with the participant.

When: This symptom survey should be completed at each visit, starting at month 1.

Directions: Begin by setting the time frame for the participant by reminding him of the date of his last T Trial visit. Ask if the participant has had any of the symptoms listed below since the last T Trial visit. If a man cannot remember or does not know the answer to one of the questions, there is an answer choice reflecting this, "Don't know." All questions should be answered by the participant.

- After the month 1 visit, refer to previous symptom forms and use your best clinical judgment to evaluate any changes in the participant's symptoms over time.

1. Cerebrovascular Symptoms (TIA and Stroke)

Q 1.b and Q 1.c. If a participant reports feeling sudden numbness or a dead feeling on both sides of the body, this should be recorded on the CVSYM CRF as 'Yes.' It should also be noted in the source document.

2. Cardiac Assessment (Angina)

Q 2.a. Ask the participant if he has had any pain or discomfort in his chest since the last visit; if "No", proceed to the next section, which focuses on congestive heart failure.

Q 2.b. If a participant records chest pain while walking uphill, or hurrying, or both, record the answer as 'Yes'. Record 'Yes' if either walking uphill *or* hurrying causes pain or discomfort.

If a participant says that he has chest pain while walking uphill but he never hurries, record the answer as 'Yes'.

Only record that participant "Never hurries or walks up hill" if he does not get chest pain because he never performs those activities.

Q 2.c. If the participant has chest pain while walking on the level, meaning on level ground, record the answer as 'Yes.'

If the answer to either question 2.b. or question 2.c. is 'Yes' then proceed to question 2.d. and continue with the survey.

If the answer to both questions 2.b and 2.c is 'No', stop the survey and proceed to the congestive heart failure symptom assessment.

Q 2.d. If the participant has chest pain while walking, record what happens. If a participant says that he continues after taking nitroglycerin, mark the answer as "Stop or slow down." Also, record this information on the Concomitant Medication form if you have not done so already.

Q 2.e. Mark all parts of the body where the participant experiences pain.

3. Cardiac Assessment (Congestive Heart Failure)

Directions: All of the questions, **3.a – 3.f**, should be answered. The one exception is question **3.c.1**, which should only be answered if question **3.c.** is 'Yes'.

4. Peripheral Vascular Disease Assessment

Directions: This is a one question survey which focuses on pain in the back of the legs as a marker of peripheral vascular disease. This question should be asked of all participants.

5. Other Symptoms

Purpose: Questions 5.a – 5.c focus on other symptoms, events, HCP, hospital and Emergency Department (ED) visits the participant may have had since his last T Trial visit. The purpose of these questions is to gather information on any other events or symptoms participants may have encountered since their last visit, which were not already recorded on the previously completed symptom surveys.

Who: These questions should be completed by the RC via an interview with the participant.

When: This symptom survey should be completed at each visit, starting at month 1.

Directions: Symptoms and events collected in this section are **not** limited to cardiovascular conditions. This form serves as the source document for completing the AE form. Collect complete information about **any** event in this section and transcribe it onto the AE CRF.

Q 5.a. Ask the participant if he has experienced any symptoms or events which adversely affected his health. If 'Yes', ask him to briefly describe the event.

Q 5.b. Ask the participant if he visited a physician or ED to seek help for *those symptoms or events*.

Q. 5.c. Ask if the participant has seen a physician or visited an ED for *any other reason*. If 'Yes,' record the details below.

4.B.1 Clinical Follow-Up

After completing the CVSYM form, the RC will assess if the participant is receiving medical follow-up for reported symptoms or changes in health status. Ask the participant if he has reported information regarding cardiovascular symptoms and events to his HCP.

If 'Yes', ask him what a physician has told him (provided a diagnosis) and whether he has started taking any new medication or is involved in a treatment plan in response to the new symptom(s). Record new medications on the CMED form. Record any other relevant treatment information in the source documents.

If 'No', inform him that you will provide this information to his HCP. (Permission to do so is indicated in the trial consent form and documented on the Randomization form.)

4.B.2 Contacting the HCP

Contact the HCP by phone, fax or email to report the symptom information, using the template **'Memo to HCP'** posted on the website. (See text below.)

If a participant is unable to identify a primary physician or HCP, the site personnel will identify a HCP at the medical institution associated with the site to evaluate the participant. The site personnel should make the appointment for this visit.

During each subsequent visit, compare the current symptom checklist and AE form to the previous forms to identify newly reported symptoms and/or changes (worsening) of pre-existing conditions. Ask the participant about the status of previously reported symptoms and record new diagnoses on the AE form. If necessary, provide additional information in the source document binder.

Instructions for completing the AE form are found in the T Trial Manual of Procedures. The template letter below may be adapted to communicate with health care providers.

4.B.3 Template Letter to Report Symptoms to HCP

Dear Dr. _____,

Your patient, *Mr.* _____, is a participant in The Testosterone Trial at [*clinical site location*]. The Testosterone Trial is a clinical trial to evaluate the effect of testosterone compared to placebo in men 65 and older.

During a Testosterone Trial study visit on *[date*], your patient reported the following:

[*cut and paste information here*].

We asked Mr. _____ to see you about these new symptoms. Please contact me if you have questions or need additional information.

Sincerely,

Site Principal Investigator

4.C Cardiovascular Event Questionnaire [CVEVENTS]

During each clinic visit, the RC will collect medical event information from each participant through the administration of the Cardiovascular Event Questionnaire [CVEVENTS]. The CVEVENTS form asks participants:

1. If a health care provider has diagnosed a new condition since the last T Trial contact.
2. If they have been hospitalized for any one of a detailed list of conditions since the last T Trial contact.
3. If they have received any one of a list of tests or procedures (as an inpatient or outpatient) since the last T Trial contact.

Purpose: To identify important cardiovascular events that occur between T Trial visits and to collect important administrative information about each event so that supporting medical record information can be collected

Who: RC completed, as a participant interview.

When: This case report form is completed at each in-person visit beginning at Month 1. In order to orient the participant to the time frame, remind him of the date of his list study visit.

Q1: This question is meant to identify new diagnoses, which *may or may not* be associated with a hospitalization or emergency department (ED) visit. A "Yes" response to this question should be indicated in the check box. If (after completing the rest of the form) it is noted that the diagnosis is *not* associated with a hospitalization or emergency department (ED) visit, this is an event that will require additional follow-up by acquiring records from the HCP's office.

Q2: These questions are meant to identify a hospitalization or emergency department (ED) visit. A "Yes" response to any of these questions should be followed by a discussion and documentation of the number of hospitalizations or ED visits, as indicated on the form.

Q3: These questions are meant to identify tests or procedures done as an inpatient or outpatient.

Important Note: In order to collect accurate data and to ensure that you are not collecting duplicative data (reported at a previous visit), the responses on this form should be compared to the previous form.

4.D Cardiovascular Event Administrative Form [CVADMIN]

The **CVADMIN** form is an administrative form used to collect complete and accurate information regarding each of the identified events. Complete a separate section for each event. This information should include:

- HCP information for diagnoses that are <u>not</u> associated with a hospitalization

- Admission and discharge dates for any hospitalizations or ED visit
- Date of the test or procedure for any diagnostic test or procedure
- Name and address of institution, test center, HCP
- Treating and ordering physician

This information should be recorded the CVADMIN (administrative) form but it is ***not*** entered into the DMS. It should only be available to clinical site personnel, as it is important Protected Health Information (PHI) and must be stored securely. It is essential that this information is recorded as accurately and completely as possible for each event. Recording accurate and complete information will make it easier and more efficient to investigate when and where events occurred and which records should be obtained.

Important Note: If a participant has a myocardial infarction or stroke, treatment will be stopped. Complete a study stop form and enter it into the data management system.

4.D.1 Obtaining medical record release consent

Participants will be asked to provide consent for site staff to access their medical records as needed. This consent will be valid for a stated period of time. If the participant's consent expires, staff must send the participant a new medical release form to obtain further permission to access medical records. The length of time that a signed consent is valid varies by institution. Site staff should follow their institution's guidelines to ensure they are implemented properly.

4.D.2 Document Checklist (DOCLIST)

Site staff will acquire copies of the medical record information associated with the event, de-identify it (redact all Protected Health Information) and send these records to the DCC with a Document Checklist.

The DOCLIST must be included as the first page to indicate the enclosed supporting documentation. Record the CVEVENT form date (visit date on which the event info was collected) that represents the event under investigation. Also record the corresponding AE sequence number for the AE form.

Depending on the event under investigation (see columns on the DOCLIST), check the box that indicates which information has been acquired form the medical record. The shaded boxes are meant to show which info may be most relevant for a given event.

5 COLLECTION OF EVENT RELATED INFORMATION

5.A *Diagnoses not Associated with a Hospitalization*

Clinical sites will investigate possible diagnoses of MI, stroke, atrial fibrillation, angina and heart failure, ***not associated*** with hospitalization or ED visit. (It is anticipated that there will be very few diagnoses not associated with hospitalization.) If a participant reports one of these conditions because his HCP informed him of this during an office visit, the clinical site staff must acquire the documentation from the HCP that supports this diagnosis.

Signed medical record release forms and HIPAA authorization forms will be required to obtain this information from HCPs, and testing/imaging facilities. A Document Checklist indicates the information that has been acquired and must accompany records. If supplemental information is unavailable from outpatient testing or from the HCP, then no further action will be required to assess this reported event.

5.B *Hospitalizations*

All reported hospitalizations on the CVEVENT form (MI, angina, heart failure, cardiac surgery, arrhythmia, stroke, carotid artery disease, peripheral arterial disease, deep vein thrombosis), including ED visits, will require investigation.

5.C *Tests and Procedures*

Sites will investigate the following tests:

(1) echocardiogram (ECHO, cardiac ultrasound tests)
(2) cardiac stress tests (e.g. with or without exercise (treadmill), pMIBI, MIBI, stress thallium, stress ECHO, dobutamine ECHO)
(3) head CT or MRI for a condition other than headache or sinus trouble.
(4) Holter monitor

These outpatient (not associated with hospitalization) tests and procedures will require completion of the CVADMIN form. The inpatient occurrences of these procedures will be investigated as part of an inpatient hospitalization.

5.D *Death*

All reported deaths will be investigated and documented on a Reported Death form [REPDEATH] by the clinical site, which includes a review of the following documents depending on availability: death certificate, autopsy/coroner's reports, and obituary. If the participant's death occurred in a hospital, the clinical site will provide the relevant hospital records to the DCC. Whenever possible, the surviving spouse or identified contact should be interviewed to try to determine the cause of death and to collect information that could lead to an event investigation.

For participants who are no longer reachable, an assessment will be initiated via the National Death Index records to attempt to identify participants who are deceased.

5.E Requesting Medical Records

During T TRIAL visits, participants will provide consent for study personnel to access their medical records as needed. This form may be valid for six months or one year, depending on institutional guidelines. It is essential to have a current signed, medical record release form in order to request medical records from a hospital medical record department.

It will be necessary to become familiar with rules governing the length of time a signed release is considered valid and to check with the major medical centers in the area to become aware of any specific policies they may have regarding a signed medical release form's expiration. Note that policies at individual hospitals may vary with respect to allowing external staff access to the records themselves. Institutional Review Board (IRB) approval may be needed to access some records. Sites should contact their institution's HIPAA official to ensure that their consent practices are appropriate.

The Document Checklist (DOCLIST) is an administrative form that will accompany hospitalization and outpatient records to indicate the accompanying data.

5.F Transferring Documents to the DCC

5.F.1 Copying Documents

Site personnel are responsible to photocopy selected parts of the medical record. (The Document Checklist indicates which sections of the record are important to include for a particular event.) This may include ECGs, MRI, CT, cardiac catheterization, consultation

reports, etc.

Protected Health Information (PHI) that is visible on the copy **must be obliterated** before sending these documents to the DCC. Documents may be scanned and transferred to the DCC on CD or paper which must be sent via traceable courier.

5.F.2 De-identifying Documents

It is very important to remove PHI before transmitting medical records to the DCC. This includes various kinds of clinical data documents, including laboratory and narrative reports. PHI on records may be removed using a software tool or manually; all records must be inspected thoroughly before transmission to the DCC.

De-identification is the process by which PHI is rendered individually unidentifiable through the removal of such identifiers. The best way to delete PHI is to use a large black marker. Photocopy the information and black it out again using the same marker. For the purpose of evaluating events, do not remove dates of service from the documents. Write the T Trial PID # at the top right corner of the page in case papers become separated.

Protected Health Information (PHI) in medical records includes the following 17 elements:

Name	Account numbers
All elements of a street address, city, county, precinct, zip code & equivalent geocodes, except for the initial three digits of a zip code for areas that contain over 20,000 people	Certificate/license numbers
Birth month and day of the individual (the year is acceptable)	License plate numbers, vehicle identifiers, and serial numbers
Telephone numbers	Device identifiers and serial numbers
Fax numbers	URL addresses
E-mail address(es)	Internet Protocol address numbers
Social security numbers	Biometric identifiers, including finger, and voice prints
Health record numbers	Full face photographic images and comparable images
Any other unique identifying number, characteristic or code except a code used for re-identification purposes	

5.F.3 Transferring documents to the DCC

Hospitalization and HCP records should be sent to the DCC with the DOCLIST as follows:

- Electronically scanned and sent to the T Trial secure file transfer server
- Electronically scanned and copied to a CD and sent via traceable courier
- Photocopied and sent via traceable courier (if unable to scan)

To send event investigation documents, complete the following steps:

- scan the entire set of documents

- the first document should be the DOCLIST
- if the event is a reported death, include the REPDEATH form
- save the file as a single .pdf with the following information in the file name:
    - 6 digit T Trial PID – CV EVENT – yyyymmdd.pdf [Use the date the CVEVENT form was completed as indicated by the date in the form header.]
    - Example: 150175-CVEVENT-20110328.pdf

5.F.4 File transfer protocol

- To be determined

See table below for an overview of Event Ascertainment Activities.

	Sequence	**Responsible Party**
1	Collect EVENT data at each participant visit on the CVEVENTS form. Identify the events that will require collection of follow-up data.	Site
2	Document related CV Event info on the CVADMIN form that will allow acquisition of medical records.	Site
3	Acquire necessary medical record release form(s).	Site
4	Enter CVEVENT and AE data into the data management system within 5 days of collection.	Site
5	Collect medical record and/or HCP data as soon as possible, ideally within 6 weeks.	Site
6	De-identify, scan records and transfer to the DCC (scan and deliver), within 8 weeks.	Site
7	Compile all data; assign, distribute and track progress of MD adjudicator.	DCC
8	Evaluate and determine event status.	DCC
9	Enter data, generate CV Events report.	DCC