

Reporting of Adverse Events to the IRB

A. BACKGROUND/PURPOSE

Investigators are required by FDA regulations to report all adverse experiences of drugs, biologics and devices occurring during the course of a study to the sponsor (21 CFR Sections 312.64(b), 812.150(a)(1)). For serious and unanticipated adverse events for drugs and biologics, investigators must report these promptly to their sponsor and reviewing IRB (21 CFR Section 312.64(b)). In addition, for device studies FDA regulations require the sponsor to report any Adverse Events (AEs) that occur during the study to all reviewing IRBs (21 CFR Section 812.150 (b)(1)).

In adherence to these regulations, the IRB process for reviewing Adverse Event reports and sponsor generated safety reports relies upon the Principal Investigator (PI) to provide critical information not easily obtainable by the CAMC/WVU IRB (IRB). The PI bears the ultimate responsibility for protecting his or her patients enrolled in clinical research.

In addition, federal regulations [21CFR56.108 (b)(1) and 45CFR 46.103(b)(5)] require the IRB to have written procedures and to follow the written procedures to ensure that Principal Investigators promptly report serious and unanticipated adverse events to the IRB. The CAMC/WVU IRB Adverse Event reporting process extends to all research carried out under its authority, whether the research is federally sponsored or not.

B. DEFINITIONS

The CAMC/WVU IRB categorizes adverse events in three ways:

1. Internal or External

-internal – includes an SAE that occurs with a subject enrolled at a study site specifically under the jurisdiction of the CAMC/WVU IRB review (e.g. CAMC, its divisions and affiliates, WVU-Charleston, etc.) NOTE: An internal SAE may occur with someone other than a subject involved in the study (e.g. study coordinator, nurse, lab technician) – these also may be reportable.

-external – includes an SAE that occurs with a subject enrolled at a study site under another IRB's jurisdiction.

2. Serious or Unanticipated

-serious – includes any experience that is fatal or life threatening, is permanently or significantly disabling, requires inpatient hospitalization or prolongation of hospitalization, a congenital anomaly/birth defect or any medical event which requires treatment to prevent one of the medical outcomes listed above.

-unanticipated – any adverse experience that is not identified in nature, severity or frequency in the consent form and is not due to a disease process.

3. All other Adverse Events

-AEs that are not serious or unanticipated (Only device study AEs are reportable to the IRB),

-SAEs that are determined by the subject's Principal Investigator/Attending Physician to be "Not Study Related," (with the exception of an Internal SAE death that is "Not Study Related")

-External SAEs that are determined to be already covered in the consent form,

-External SAEs that occurred on another protocol using the same or similar investigational device/drug/procedure.

Resource for Federal Definitions:

Location of Specific FDA Definitions of AEs for Drug Studies – 21 CFR Section 312.32(a)

Location of Specific FDA Definition if AEs for Device Studies – 21 CFR Section 812.3(s)

C. IRB Requirements for Reporting Serious Adverse Events (SAE's)

1. Timelines:

- In general, Principal Investigators are required to report serious and unanticipated adverse events (SAE's) that are study related or possibly study related to the IRB within 10 working days after first awareness of the event.
- Internal deaths must be reported via email or telephone to the IRB office within 24 hours after the first awareness of the event, and then formally submitted in writing within 10 working days after first awareness of the event.
- All other SAEs are to be entered onto a tracking log as they are received. This log is submitted to the IRB with each SAE submission and at the time of continuing renewal and closure of the study.
- AEs on device studies are to be tracked and submitted to the IRB only at the time of renewal. These do not need to be submitted on the SAE Tracking Log. They may be submitted in the same format sent to the sponsor or in another listing developed by the PI and/or study coordinator.

2. Forms:

All SAEs are to be reported using the required CAMC/WVU IRB Instructions, Forms and SAE Tracking Log. The instructions and forms are available by contacting the CAMC/WVU IRB through the CAMC Institute Office of Research and Grants Administration.

D. IRB Review of an SAE:

The IRB staff is responsible for the initial assessment of the SAE reports to determine the level of review necessary. SAEs that require further review will initially be sent to two members of the IRB for expedited review. Based on the decision of the two members, the SAE may then need to be sent on for full board review. After the review is completed, the investigator will receive either a letter or a stamped SAE form indicating the decision of the IRB. Note: If the two IRB members agree on a change to the consent, the PI will be sent a letter requesting the change and full board review will not be required. If the staff and/or IRB members agree that an internal SAE is already covered in the consent form, the SAE will be returned as "Reviewed no further action necessary." Turn-around time on the SAE varies depending on the level of review. A summary of SAE reports qualifying for expedited review will be included on the Expedited List for review at the next convened IRB meeting.

As a way to ensure the protection of human subjects enrolled in research and to monitor the risk/benefit ratio related to SAEs, the IRB has the authority to:

- Require a change in the protocol and/or the consent document.
- Require notification to subjects previously enrolled in the study that a SAE has occurred.
- Require the re-consent of currently enrolled study subjects.
- Suspend or terminate the protocol. A decision to suspend or terminate approval by the IRB shall be reported in writing to the investigator, and when necessary, appropriate institutional officials and the FDA.

E. RESPONSE TO IRB DETERMINATION OF SAE

Upon notification, the PI is required to make any necessary revisions to the protocol and/or consent/assent document and forward the revised original document(s) to the IRB Office for approval. Failure to make the revisions could result in suspension of the research protocol.

F. REPORTING OF SAEs ON CONTINUING RENEWAL REPORT

The PI is required to report all SAE's with the continuing review progress report by using the SAE Tracking Log. Failure to include a reported SAE with the progress report could result in suspension of the research protocol (note: device studies should also include a listing of all AEs). Also at the time of study renewal, a copy of the most recent Data Safety Monitoring Board (DSMB) report for the study (if applicable) is to be submitted for IRB review.

(Revised 2/22/2004)

CAMC/WVU IRB INSTRUCTIONS FOR REPORTING ADVERSE EVENTS

A. PRINCIPAL INVESTIGATOR GENERAL RESPONSIBILITY:

Essential to the effectiveness of the adverse event (AE) review is the CAMC/WVU IRB (IRB) reliance on the expertise of the principal investigator (PI). The PI is required to review each serious or unanticipated AE (SAE) in terms of its relationship to the study and to address possible changes in the risk-benefit ratio that may necessitate changes in the protocol and/or consent form. While study coordinators and research assistants may assist in processing the SAE submission to the IRB, the PI has the ultimate responsibility of determining whether or not the risk/benefit ratio of the research continues to be acceptable.

B. REPORTING REQUIREMENTS:

Definitions:

The IRB categorizes adverse events in three ways:

1. Internal or External
2. Serious or Unanticipated
3. All other Serious Adverse Events and AEs for device studies

The IRB definitions of internal and external adverse events are as follows:

- internal** – includes an SAE that occurs with a subject enrolled at a study site specifically under the jurisdiction of the CAMC/WVU IRB review (e.g. CAMC--its divisions and affiliates, WVU-Charleston, etc.) NOTE: An internal SAE may occur with someone other than a subject involved in the study (e.g. study coordinator, nurse, lab technician) – these also may be reportable.
- external** – includes an SAE that occurs with a subject enrolled at a study site under another IRB's jurisdiction. (NOTE: If your study is not a multi-center study and was reviewed by the CAMC/WVU IRB, all of your events are internal.)

The IRB definitions of serious and unanticipated adverse events (SAEs) are as follows:

- serious** – includes any experience that is fatal or life threatening, is permanently or significantly disabling, requires inpatient hospitalization or prolongation of hospitalization, a congenital anomaly/birth defect or any medical event which requires treatment to prevent one of the medical outcomes listed above.
- unanticipated** – any adverse experience that is not identified in nature, severity or frequency in the consent form and is not due to a disease process.

(NOTE: Serious Adverse Events that do not meet these definitions will be reported to the IRB only through the SAE Tracking Log – more information on this is listed below.)

The IRB definitions of all other Serious Adverse Events are as follows:

- AEs that are not serious or unanticipated (Only device study AEs are reportable to the IRB),
- SAEs that are determined by the subject's Principal Investigator/Attending Physician to be "Not Study Related," (with the exception of an Internal SAE death that is "Not Study Related")
- External SAEs that are determined to be already covered in the consent form,
- External SAEs that occurred on another protocol using the same or similar investigational device/drug/procedure.

Submission timelines:

In general, PIs are required to report serious or unanticipated adverse events (SAEs) to the IRB **within 10 working days after first awareness** of the event. If for any reason the report cannot be submitted within this timeframe, please notify the IRB office (e.g. you are awaiting a discharge summary report or death certificate, etc.)

The one exception to the 10 working day requirement is that of **internal deaths**. Please notify the IRB via email or telephone **within 24 hours** after the PI/Study Coordinator is made aware of the death, and if possible at that time, indicate to the IRB if the death is study related or not study related. All other submission requirements on the internal death will then be due within 10 working days after first awareness of the event.

Reporting of Adverse Events to the IRB

All other SAEs (not AEs), (*defined above) are to be entered onto the Serious Adverse Event (SAE) Tracking Log **as they are received**. The tracking log must then be submitted to the IRB with each new SAE submission and also with the Continuing Review/Study Closure submissions. Note: Device studies should also submit a listing of all AEs at the time of Continuing Review.

(CAUTION: Because the IRB may request this SAE Tracking Log at any time, it is important that you keep the log up-to-date as you receive the SAEs. Also, at any point, the IRB may ask for additional materials about any SAE listed on the log.)

Submission Process:

*For **Internal Serious or Unanticipated Adverse Events that are determined by the subject's Principal Investigator/Attending Physician to be Study Related or Possibly Study Related and all Internal study subject deaths:*** Report these to the IRB using **Form #SAE-01 Internal** and the **SAE Tracking Log**.

*For **External Serious or Unanticipated Adverse Events that are determined by the subject's Principal Investigator/Attending Physician to be Study Related or Possibly Study Related and are NOT already covered in the consent form:*** Report these to the IRB using **Form # SAE-02 External** and the **SAE Tracking Log**.

*For all **other *SAEs:*** Report these to the IRB using the **SAE Tracking Log** only.

**-SAEs that are determined by the subject's Principal Investigator/Attending Physician to be "Not Study Related," (with the exception of an Internal SAE death that is "Not Study Related")*

**-External SAEs that are determined to be already covered in the consent form,*

**-External SAEs that occurred on another protocol using the same or similar investigational device/drug/procedure,*

-AEs that are not serious or unanticipated – **for device studies only—keep on a separate listing (usually as required by the sponsor) and report to the IRB only at the time of Continuing Review.*

C. FORMS:

Form # SAE-01 Internal and **Form # SAE-02 External** and the **SAE Tracking Log** are available at the department web site (<http://www.camcinstitute.org/Research/grants.htm>) and by contacting the CAMC/WVU IRB at 304-388-9971.

Form # SAE-01 Internal and **Form # SAE-02 External:** These forms ask for specific information about the study and SAE. In addition, supporting materials for the SAE should be attached with the form and tracking log (e.g. any relevant paperwork received from the attending physician, the sponsor, the FDA, the hospital(s) concerning the SAE or any paperwork submitted by the PI or Study Coordinator to the sponsor and/or FDA concerning an internal SAE. Examples of items to include are the operative reports or discharge summaries. Do not include daily chart summaries/reports.). **NOTE: Please de-identify the accompanying paperwork – no patient identifiers should be sent to the IRB!**

SAE Tracking Log: The purpose of the SAE Tracking Log is to aid the Principal Investigator and the IRB in tracking possible trends with all serious and unanticipated adverse events on a study in order to continually monitor the risk/benefit ratio. **Please maintain a log for each study, listing all SAEs in chronological order.** A sample of an **SAE Tracking Log** is attached to these instructions. All of the elements listed in the sample log are required; however, the PI may add other elements as necessary.

Forms and all necessary attachments (INCLUDING THE MOST RECENTLY APPROVED CONSENT FORM) should be completed and submitted according to the timelines listed above. It is important to communicate with the IRB office if forms cannot be completed within the designated timeline.

D. OTHER GENERAL INFORMATION:

At the same time an internal SAE is reported to the FDA or the study sponsor, also submit completed IRB SAE report forms and the log to the CAMC/WVU IRB.

SAE submissions must also include a copy of the most recently approved consent form. Your submission will be returned if the consent is not attached.

To aid in tracking the original document, the IRB requires that internal departments (e.g. Clinical Trials Center, Cancer Research Center, etc) use yellow paper for **Form # SAE-01 Internal** and **Form # SAE-02 External**. We understand that all departments may not have access to yellow paper and we will be flexible.

Follow-up and Final reports for SAEs should be handled in the same way as initial submissions.

For studies that remain open for long-term follow-up purposes only (no further subject treatment or protocol specific follow-up), internal deaths that are disease related are not considered reportable to the IRB.

SAE reports that do not provide enough information to determine that foreseeable risks exist will be returned to the PI with a determination of “insufficient data.”

Once a study is in the data analysis phase (no subject contact whatsoever) or once a study has been CLOSED (or withdrawn/ terminated) at this site, the IRB is no longer required to take action on serious adverse event reports. However, these SAE reports must still be submitted to the IRB according to the above instructions. The report will then be filed with the study information in the IRB office. A copy will be stamped and returned to the PI/Study Coordinator as reviewed/no further action necessary, unless the IRB would note a serious issue that warrants attention.

All questions in the SAE Forms may not apply to each study, particularly if the study is not clinical in nature. In this instance, the PI/Study Coordinator should complete all applicable information on the appropriate SAE form and the log, and then attach a cover letter if further clarification about the SAE is needed to explain the SAE to the IRB.

Turn-around time for Serious Adverse Event review by the IRB varies depending on whether or not the SAE warrants a full board review after the initial staff review/IRB expedited review.

Submit the **original** SAE reports and a copy of the log (with supporting materials and consent) to the CAMC/WVU IRB, Room 3283, 3110 MacCorkle Avenue, SE, Charleston, WV 25304. Faxed reports will be accepted only in rare instances. If you have questions, please call 304-388-9971.

CAMC/WVU IRB ADVERSE EVENT SUBMISSION GUIDE
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ADVERSE EVENT	SUBMIT TO IRB ON A FORM	TRACKING LOG
Internal Death All Deaths Whether or Not Study Related	X	X
Internal SAE's Possibly Study Related or Study Related	X	X
Internal SAE's Not Study Related		X
Internal SAE's Possibly Study Related or Study Related Covered or Not covered in the Consent Form	X	X
Internal AEs for Device Studies AEs not serious or unanticipated		X Can be kept on separate log
External SAE's Not Study Related		X
External SAE's Possibly Study Related or Study Related and Covered In the Consent Form		X
External SAE's Possibly Study Related or Study Related, and NOT Covered in Consent Form	X	X
External SAE's Occurring on Another Protocol Using the Same Device/Drug/Procedure		X
External AE's for Device Studies AEs not serious or unanticipated		X Can be kept on separate log

(Revised 2/22/04)

Received: _____
IRB Processed: _____
H.S. #: _____
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CAMC/WVU IRB HUMAN SUBJECTS SERIOUS ADVERSE EVENT REPORT FORM Internal Serious or Unanticipated Adverse Event

Please refer to the “Instructions for Reporting Adverse Events” for a complete explanation of the CAMC/WVU IRB adverse event reporting process.

Federal guidelines require timely reporting (we define this as within 10 working days after first awareness of the event) of unanticipated or serious adverse events (SAE) (21CFR56.108.b.1) in accordance with the IRB written procedures (45CFR46.103.b.5). (*Please see the bottom of this form for definitions of “serious” and “unanticipated.”) This form is to be used to report internal serious or unanticipated events that are determined by the subject’s Principal Investigator/Attending Physician to be study related or possibly study related, and to report any case of an internal death (study related or not) of a study subject. All SAEs must also be included on the SAE Tracking Log.

All internal deaths in studies must be reported using this form and the SAE Tracking Log. However, in the case of any internal death of a study subject, please notify the IRB via email or telephone within 24 hours after you are made aware of the death, and if possible at that time please indicate if the death is study related. This form and accompanying materials would then be due within 10 working days.

If the internal SAE is determined by the subject’s Principal Investigator and/or Attending Physician to be “Not Study Related” and is not a death, please do not complete this form. Instead add the SAE to the SAE Tracking Log.

NOTE: If additional space is needed for answering any of the following questions, please attach additional pages. Also, be sure to attach supporting materials and a copy of the most recently stamped approved consent form. If your study is not clinical in nature and certain questions do not pertain to your study indicate “not applicable” next to the question.

I. GENERAL INFORMATION:

1. Principal Investigator: _____
2. Research Coordinator: _____
3. Study HS #: _____
4. Study Title: _____
5. Is the study permanently closed to enrollment? [] Yes [] No If yes, provide date: _____
6. Are any subjects at this site still on study treatment? [] Yes [] No If yes, how many? _____
In follow-up? [] Yes [] No If yes, how many? _____
7. How many subjects have been enrolled at this site since initial study approval: _____
8. If this is a multi-site study, include total number of subjects at all sites:
(do not put unknown – form will be returned)

II. SPECIFIC SAE INFORMATION:

1. Subject’s identifying number/initials: _____
2. Date SAE reported to sponsor: _____ FDA: _____ (if applicable)

Reporting of Adverse Events to the IRB

3. Date SAE occurred: _____ Date SAE ended: _____ Duration if less than 24 hours: _____ Ongoing? Yes [] No []
4. Describe the SAE -- briefly (e.g. renal failure, heart palpitations, convulsions):
5. Was this event expected within the scope of the subject's medical history? [] Yes [] No
If yes, explain:
6. Did this event result in the subject's withdrawal from the study? Yes [] No []
If yes, the withdrawal was due to: [] Death [] Medically indicated [] Patient or Physician Request
7. Date of initial use of investigational study drug/device/procedure: _____ (If applicable)
(example: date of surgery when device implanted, date study drug initially administered, etc.)
If study drug, ongoing? [] Yes [] No If no, date ended: _____
8. Check all that apply:
 Resulted in hospitalization or prolonged hospitalization Resolved Ongoing
 Resulted in permanent disability
 Resolved spontaneously
 Resolved with treatment
 Subject died Autopsy performed? [] Yes [] No
9. Is this event already included in the consent form? [] Yes [] No
(NOTE: Internal SAEs that are already covered in the consent will likely receive administrative review only)
If yes, please indicate where (e.g. consent version date 12/5/03, Risk section under Rare, Page 5): _____
10. Relationship to study drug/device, in investigator's opinion (to be determined by the Principal Investigator and/or attending physician):
(Check one)
 Study-Related (this category can include a death)
 Possibly Study-Related (this category can include a death)
 Death – Not Study-Related
 (Please note: The IRB does not give a separate review to SAEs that are determined by the subject's Principal Investigator/Attending Physician to be "Not Study Related". However, these should be listed on the SAE Tracking Log. In addition, all internal deaths are to be reported whether considered study related or not.)
11. Have similar SAEs been reported previously? Yes No
If yes and if available, what is the number of times the event has occurred at this site: _____ study-wide: _____
12. Are you requesting a consent form and/or protocol change as a result of this event in order to reduce or eliminate risk?
 Yes No
If yes, please submit the changes using the standard full board amendment process and attach this report as supporting material for the amendment. In your judgment if a change in the consent form and/or protocol is not warranted, please give a brief explanation:
13. Should currently enrolled subjects be informed of this event? Yes No
If yes, please describe the method(s) to be used to inform patients of this event and, if applicable, attach for review and approval a copy of any written materials you propose should be sent to subjects:
14. Has this SAE already been submitted under an initial or follow-up report? [] Yes [] No If yes, please indicate the date it was submitted to the IRB _____. Have you received a response from the IRB yet on the initial or follow-up report? [] Yes [] No If yes, what date was the approval? _____

Principal Investigator's Signature

Date

***Definitions:**

-serious – includes any experience that is fatal or life threatening, is permanently or significantly disabling, requires inpatient hospitalization or prolongation of hospitalization, a congenital anomaly/birth defect or any medical event which requires treatment to prevent one of the medical outcomes listed above.

Reporting of Adverse Events to the IRB

-unanticipated – any adverse experience that is not identified in nature, severity or frequency in the consent form and is not due to a disease process.

Received: _____
IRB Processed: _____
H.S. #: _____
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CAMC/WVU IRB HUMAN SUBJECTS SERIOUS ADVERSE EVENT REPORT FORM

External Serious or Unanticipated Adverse Event

Please refer to the “Instructions for Reporting Adverse Events” for a complete explanation of the CAMC/WVU IRB adverse event reporting process.

Federal guidelines require timely reporting (we define this as within 10 working days after first awareness of the event) of unanticipated or serious adverse events (SAE) (21CFR 56.108.b.1) in accordance with the IRB written procedures (45CFR46.103.b.5). (*Please see the bottom of this form for definitions of “serious” and “unanticipated.”) This form is to be used to report external serious or unanticipated events that are determined by the subject’s Principal Investigator/Attending Physician to be study related or possibly study related. All SAEs must also be included on the SAE Tracking Log.

If the external SAE is determined by the subject’s Principal Investigator and/or Attending Physician to be “Not Study Related,” please **DO NOT COMPLETE THIS FORM**. Instead add the SAE to the SAE Tracking Log.

If the external SAE is already covered in the consent form, **DO NOT COMPLETE THIS FORM**. Instead add the SAE to the SAE Tracking Log.

If the external SAE occurred on another protocol using the same or similar investigational device/drug/procedure, **DO NOT COMPLETE THIS FORM**. Instead add the SAE to the SAE Tracking Log.

NOTE: If additional space is needed for answering any of the following questions, please attach additional pages. Also, be sure to attach supporting materials and a copy of the most recently stamped approved consent form. If your study is not clinical in nature and certain questions do not pertain to your study indicate “not applicable” next to the question.

I. GENERAL INFORMATION:

1. Principal Investigator: _____
2. Research Coordinator: _____
3. Study HS #: _____
4. Study Title: _____
5. Is the study permanently closed to enrollment? [] Yes [] No If yes, provide date: _____
6. Are any subjects at this site still on study treatment? [] Yes [] No If yes, how many? _____
In follow-up? [] Yes [] No If yes, how many? _____
7. How many subjects have been enrolled at this site since initial study approval: _____
8. If this is a multi-site study, include total number of subjects at all sites:
(do not put unknown – form will be returned)

II. SPECIFIC INFORMATION:

1. SAE Sponsor Tracking Number (Use Subject Code if no tracking number available): _____
2. Date SAE reported to sponsor: _____ FDA: _____ (if applicable)
3. Date SAE occurred: _____ Date SAE ended: _____
If known, duration if less than 24 hours: _____ If known, is SAE ongoing? Yes [] No []

Reporting of Adverse Events to the IRB

4. Describe the SAE -- briefly (e.g. renal failure, heart palpitations, convulsions):

5. Check all that apply:

- Resulted in hospitalization or prolonged hospitalization
- Resulted in permanent disability
- Resolved spontaneously
- Resolved with treatment
- Subject died Autopsy performed? Yes No

6. Relationship to study drug/device, as determined by the **subject's** Principal Investigator and/or attending physician:
(Check one)

Study-Related

Possibly Study-Related

Undetermined (Note: if the designation is "undetermined" the report will likely be returned due to "insufficient data to determine foreseeable risk" and a copy will be filed in the IRB study file)

(Please note: The IRB does not give a separate review to SAEs that are determined by the subject's Principal Investigator/Attending Physician to be "Not Study Related". However, list these on the SAE Tracking Log.)

7. Have similar SAEs been reported previously? Yes No

If yes and if available, what is the number of times the event has occurred study-wide: _____

8. Are you requesting a consent form and/or protocol change as a result of this event in order to reduce or eliminate risk?

Yes No

If yes, please submit the changes using the standard full board amendment process and attach this report as supporting material for the amendment. In your judgment if a change in the consent form and/or protocol is not warranted, please explain:

9. Should currently enrolled subjects be informed of this event? Yes No

If yes, please describe the method(s) to be used to inform patients of this event and, if applicable, attach for review and approval a copy of any written materials you propose should be sent to subjects:

10. Has this SAE already been submitted under an initial or follow-up report? Yes No If yes, please indicate the date it was submitted to the IRB _____. Have you received a response from the IRB yet on the initial or follow-up report? Yes No If yes, what date was the approval? _____

Principal Investigator's Signature

Date

***Definitions:**

-serious – includes any experience that is fatal or life threatening, is permanently or significantly disabling, requires inpatient hospitalization or prolongation of hospitalization, a congenital anomaly/birth defect or any medical event which requires treatment to prevent one of the medical outcomes listed above.

-unanticipated – any adverse experience that is not identified in nature, severity or frequency in the consent form and is not due to a disease process.