



1. Purpose

The purpose of this operating procedure is to outline the process the Methods Centre (MC) follows for identifying and processing serious adverse event (SAE) information reported during the conduct of a research study.

2. Responsibilities

Research Site: The research site is responsible for reporting all SAEs as soon as possible after being made aware of the occurrence of an event and following the procedures outlined below regarding follow-up.

CERU: CERU is responsible for processing the SAE report information and following up with the research site and governing regulators as necessary.

3. Procedures

Adverse Events

- 3.1 Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with this treatment.
- 3.2 Given the high acuity of diseases and comorbidities related to critical illness, AEs are a frequent complication of critical illness. Typically CERU trials do not require research sites to report AEs, rather, specific AEs, such as infections, will be captured with the data collection procedures. Each research site will need to adhere to local ethics guidelines for reporting adverse events locally.
- 3.3 The need to capture AEs and report these to CERU will be decided on a case by case basis for each study.

Serious Adverse Events

- 3.4 A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose:
 - 3.4.1 Results in death
 - 3.4.2 Is life-threatening (refers to an event in which the study participant was, in the opinion of the qualified investigator (QI), at risk of death from the event if medical intervention had not occurred. NOTE: This does not include an event that hypothetically had it occurred in a more serious form, might have caused death).
 - 3.4.3 Requires in patient hospitalization or prolongation of existing hospitalization
 - 3.4.4 Results in persistent or significant disability/incapacity (i.e. a substantial disruption in an individual's ability to conduct normal life functions)
 - 3.4.5 Is a congenital anomaly or birth defect



Serious Adverse Event Recognition and Reporting

302-01

- 3.4.6 Other medically important condition (Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious events when, based on medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above).
- 3.5 The study protocol should outline any other criteria that should be used to determine SAEs for a specific study.
- 3.6 The research site should report a new SAE to CERU immediately following knowledge of the occurrence of the event (no later than 24 hours or as otherwise specified in the protocol).
- 3.7 Unless otherwise noted in a study specific procedures, the research site will complete a study specific SAE Report Form, and fax the information to CERU.
- 3.8 The SAE Report Form will contain, at a minimum, the following fields:
 - 3.8.1 Study ID
 - 3.8.2 Participant ID (enrolment number or randomization number)
 - 3.8.3 Participant age
 - 3.8.4 Participant sex
 - 3.8.5 Name of event being reported
 - 3.8.6 Reason for reporting the event (i.e. SAE criteria)
 - 3.8.7 Date/time of onset
 - 3.8.8 Expectedness of the event
 - 3.8.9 Relationship to investigational product
 - 3.8.10 Study treatment code (if unblinded)
 - 3.8.11 Treatment for the event
 - 3.8.12 Cause attributed to the event
 - 3.8.13 Participant status in study
 - 3.8.14 Outcome
- 3.9 The research site should also report the SAE to their local Research Ethics Board (REB) using established forms and policies at the local institution.
- 3.10 Upon receipt of the SAE information, the CERU Project Leader, or delegate, will review the information on the SAE report for completeness and medical coherency.
- 3.11 CERU will communicate with the research site to resolve any outstanding SAE report information and to discuss any ambiguities in the information provided.
- 3.12 All SAEs must have an assessment concerning the relationship to investigational product determined by the site Qualified Investigator, or medically qualified designate.
 - 3.12.1 Definitions for research sites to use to determine the relationship to investigational product will be provided by CERU.
 - 3.12.2 Definitions will be categorized into two groups: related and unrelated.



Serious Adverse Event Recognition and Reporting 302-01

3.12.3 In the absence of a relationship to investigational product determination, or if there is any doubt concerning the relationship assessment, the relationship should be considered “related” to the investigational product.

3.13 CERU will track individual SAE reports and forward onto study stakeholders as appropriate (e.g. Data Safety Monitoring Committee, manufacturer, etc) as per study specific procedures.

Expedited Reporting

3.14 Unless otherwise specified, in accordance with regulations, CERU will determine whether expedited reporting to Health Canada and other governing regulators is required in the following manner:

3.14.1 The event must meet the criteria for a “serious” adverse event.

3.14.2 There must be a suspicion of a relationship with the investigational product.

3.14.3 The reported event must be a serious unexpected adverse event (i.e. not consistent with information found in the current Investigator’s Brochure or Product Monograph).

3.15 Expedited SAEs are considered supplemental information to the existing product monograph.

3.15.1 At a minimum, CERU must report the following information to the governing regulators:

3.15.1.1 Participant ID

3.15.1.2 Identifiable reporter (i.e. name/title of the individual reporting the SAE).

3.15.1.3 Serious Adverse Event term

3.15.1.4 Investigational Product (blinded)

3.16 Refer to specific guidelines from each applicable governing regulator regarding timelines for reporting (refer to Appendix 5.3). Health Canada requires expedited reports within the following timelines:

3.16.1 Death or Life-threatening: initial report within 7 calendar days, follow-up report within an additional 8 calendar days, subsequent follow-ups as soon as possible.

3.16.2 All other SAEs: initial report within 15 calendar days, follow-up report as soon as possible.

3.17 Blinded expedited SAE reports will be forwarded to all research sites, within 15 days of receipt of site information, for notification to their respective REBs.

3.18 Blinded expedited SAE reports will be provided to Health Canada in the CIOMS I Form format (refer to Appendix 4.4). Expedited reports will be provided to the US FDA in the MedWatch Form (refer to Appendix 4.5). Refer to specific requirements from other governing regulators when determining the appropriate reporting format.

Unblinding

3.19 There may be instances when the safety of the participant is dependent on knowing which treatment arm they were randomized to.

3.20 The circumstances under which unblinding may be required are study specific, hence a Work Instruction or Study Procedures Manual should provide study specific guidelines on how to deal with



Serious Adverse Event Recognition and Reporting 302-01

unblinding. If a Data Monitoring Committee (DMC) has been established for the study, the DMC should be involved in the development of this process.

3.21 In the event that the study participant treatment code must be revealed for safety reasons, study specific procedures should be followed in addition to SOP 304: Study Treatment Code Unblinding.

3.21.1 In the event that an SAE deemed to be expeditable is unblinded, the study treatment code information should be forwarded to Health Canada and other governing regulators, as applicable, with the SAE report.

3.22 Any study participant who experiences an SAE should be followed by the research site until the first of the following occurs:

3.22.1 The event resolves.

3.22.2 An outcome is reached.

3.22.3 The event is otherwise explained or stabilized.

3.23 The research site should provide CERU with follow-up SAE Reports until one of the criteria in 3.19 is fulfilled.

3.24 CERU will maintain a SAE tracking log for all protocol specified SAE reports occurring during the clinical trial.

3.25 CERU will maintain all SAE reports and associated documentation (i.e. reports and communications, including faxes, telephone calls and instructions given) in the study files.

Periodic Safety Reports

3.26 CERU will provide Periodic Safety Reports to Health Canada and other governing regulators, study stake holders and research sites in the following circumstances:

3.26.1 Updated safety information is received from the investigational product manufacturer.

3.26.2 Following review of safety data by the Data Monitoring Committee

3.26.3 Annually

3.26.4 Research sites should submit Periodic Safety Reports to their local REBs. All related documentation should be filed by the site.

4. Appendix

4.1 Sample SAE Report Form

4.2 Sample SAE Processing Flowchart

4.3 Expedited Reporting Timelines Table

4.4 CIOMS I Form

4.5 US FDA MedWatch Form



Serious Adverse Event Recognition and Reporting
302-01

5. References

- 5.1 ICH GCP topic E2A Clinical Safety Data Management : Definitions and Standards for Expedited Reporting
- 5.2 Food and Drug Regulations Division 5: Drugs for Clinical Trials Involving Human Subjects Section C.05.014.
- 5.3 Network of Networks Standard Operating Procedures for Clinical Research (N₂ organization).

Appendix 4.1

The REDOXS[®] Study

Serious Adverse Events (SAE) - Initial Report

Complete and fax the INITIAL report to CERU at 613 548 2428 attention: Project Leader within **24 hours** of becoming aware of the event. Complete one form for **EVERY** adverse event that is Serious and Unexpected. Report only those SAEs that occur from the time of randomization to the end of the study period (30 days from admission to ICU or until ICU discharge or death, whatever comes first)

Patient Information

Site number Initials Male Height (cm) Name of Site Investigator SAE #

Enrolment # DOB Female Weight (kg) Person Reporting SAE Record the sequential SAE # for the patient i.e. for 1st SAE for this patient, write 01; For 2nd SAE for this patient, write 02.

Serious Adverse Event Reported (only one per form) Date SAE reported

Date became aware of SAE

Seriousness (select all that apply)

- Patient died --> please document date in Outcomes
- Life threatening
- Requires or prolongs hospitalization
- Results in persistent or significant disability/incapacity
- May require medical or surgical intervention to prevent one of other outcomes.

Outcomes (at the time of initial report) - select only one

- Complete recovery/return to baseline - Date of recovery
- Alive with sequelae
- Death - death date
- SAE persisting
- Unknown/lost to follow-up

Action taken (select all that apply)

- None
- Uncertain
- Procedure or physical therapy
- Blood or blood products
- Prescription drug therapy
- Non-prescription drug therapy
- Hospitalization
- IV fluids
- Other

Action taken with Study supplements (select only one)

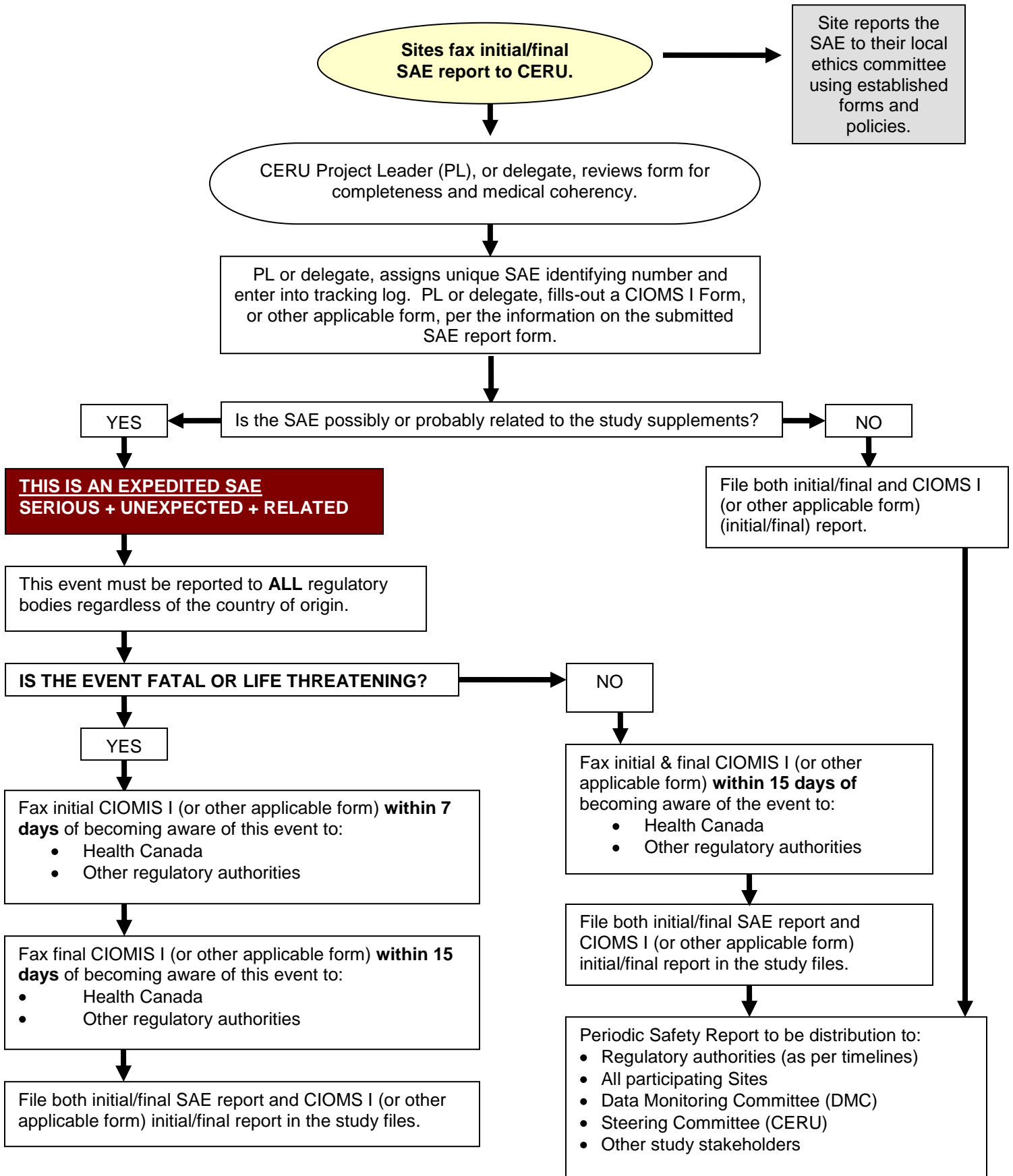
- None (including not on study supplements)
- Dose reduced, interrupted or therapy delayed
- Study Supplements stopped permanently due to SAE

Relationship of SAE to Study Supplements

- Not related
- Unlikely related
- Possibly related
- Probably related

	Date (dd/mm/yyyy)	Time (hh:mm)
Onset of SAE	<input type="text"/>	<input type="text"/>
ICU admission	<input type="text"/>	<input type="text"/>
Start of study supplements	<input type="text"/>	<input type="text"/>
Stop of study supplements	<input type="text"/>	<input type="text"/>
Signature of Site Investigator	<input type="text"/>	
Date	<input type="text"/>	

SAMPLE



Appendix 4.3

Expedited Reporting Timelines for SAEs to Governing Regulatory Authorities

Country	SAE Criteria (unexpected + related to investigational product)	Reporting Details	Reporting Format
Canada	Death or Life-threatening	Authority: Health Canada Initial Report: 7 calendar days Follow-up: 15 calendar days	CIOMS I Form
Canada	Requires in patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly or birth defect or other medically important conditions.	Authority: Health Canada Initial Report: 15 calendar days Follow-up: As soon as available	CIOMS I Form
United States	All SAEs	Authority: Food and Drug Administration Initial Report: 15 days Follow-up: As soon as possible	MedWatch Form Must be in English.
Other Countries	Refer to country specific regulations regarding when an expedited report should be reported to the applicable authorities.	To be determined by the governing authority.	To be determined by the governing authority.

* All reporting times (i.e. initial and Follow-up) are from the time CERU first becomes aware of the event.

† All reports are submitted to the regulatory authority in a blinded fashion unless the patient was unblinded for safety reasons.

Appendix 4.4

SUSPECT ADVERSE REACTION _____

of the Principal Investigator by:

**Clinical Evaluation Research Unit
Kingston General Hospital
76 Stuart Street, Angada 4, Kingston, ON K7L 2V8**

SAE # _____

I. EVENT DESCRIPTION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE YRS	3. SEX	4-6 reaction onset			8-12 CHECK ALL APPROPRIATE TO EVENT:
		day	month	year			day	month	year	
DESCRIBE EVENT:										<input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING <input type="checkbox"/> MEDICALLY SIGNIFICANT
Study Title: The REDOXS® Study: A randomized trial of Glutamine and antioxidant supplementation in critically ill patients.										
Event Name:										
13. RELEVANT TESTS/LABORATORY DATA										

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) Blinded: Antioxidant; Glutamine; Antioxidant and Glutamine; or Placebo		20. DID EVENT ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N/A
15. DAILY DOSE 	16. ROUTE OF ADMINISTRATION I.V. Infusion and/or feeding tube	21. DID EVENT REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N/A
17. INDICATION(S) FOR USE Organ failures		
18. THERAPY DATES (From/To)	19. THERAPY DURATION	

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat the adverse event)
23. OTHER RELEVANT HISTORY

IV. MANUFACTURER

24a NAME & ADDRESS OF MANUFACTURER		Company Remarks:
Study No.:	24b MFR CONTROL NO.	
Patient No.:		
24c DATE RECEIVED BY MANUFACTURER	24d REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL	
DATE OF THIS REPORT:	25a REPORT TYPE: <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP <input type="checkbox"/> FINAL	

SAE reported by:	
Site Investigator causality assessment:	
Sponsor assessment of causality (check one)	Agree <input type="checkbox"/> Disagree <input type="checkbox"/> <input type="checkbox"/> The data reviewed <u>does not</u> represent a new safety risk that warrants a change to the study protocol or consent form. <input type="checkbox"/> The data reviewed <u>does</u> represent a new safety risk that warrants a change to the study protocol or consent form. <u>Additional Sponsor Comments:</u>

Appendix 4.5

Print Next Page Reset Form Delete Page Delete Multiple Pages

Form Approved OMB No. 0910-0201, Expires 12/31/11
See OMB 0480-0045 for details

U.S. Department of Health and Human Services
Food and Drug Administration

For use by healthcare providers, importers, distributors and manufacturers for MANDATORY reporting

MEDWATCH

FORM FDA 3500A (10/09)

General Instructions

Page 1 of

MF Report #
Off/Import Report #
FDA Use Only

A. PATIENT INFORMATION		Section A - Help	
1. Patient Identifier	2. Age at time of Event: or Date of Birth:	3. Sex: <input type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight: or Height:
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
Section B - Help			
1. <input type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defect/malfunction)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (month/year)		<input type="checkbox"/> Disability or Permanent Damage	
<input type="checkbox"/> Life-threatening		<input type="checkbox"/> Congenital Anomaly/Birth Defect	
<input type="checkbox"/> Hospitalization - initial or prolonged		<input type="checkbox"/> Other Serious (Important Medical Events)	
<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Device)			
3. Date of Event (month/year)		4. Date of This Report (month/year)	
5. Describe Event or Problem			
6. Relevant Tests/Laboratory Data, including Dates			
7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergy, renal, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			

C. SUSPECT PRODUCT(S)		Section C - Help	
1. Name (include strength & formulation)			
#1			
#2			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) (month/year)	
#1		#1	
#2		#2	
4. Diagnosis for Use (indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1		#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2		#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #		7. Exp. Date	
#1		#1	
#2		#2	
8. NDC# or Unique ID		9. Event Recurred After Reintroduction?	
#1		#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2		#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
10. Concomitant Medical Products and Therapy Dates (exclude treatment of event)			
D. SUSPECT MEDICAL DEVICE			
Section D - Help			
1. Brand Name			
2. Common Device Name			
3. Manufacturer Name, City and State			
4. Model #		5. Operator of Device	
		<input type="checkbox"/> Health Professional	
		<input type="checkbox"/> Lay User/Patient	
		<input type="checkbox"/> Other:	
6. Lot #		7. Exp. Date (month/year)	
#1		#1	
#2		#2	
8. If Explained, Give Date (month/year)			
9. Is this a Single-use Device that was Reprocessed and Reused on a Patient?			
<input type="checkbox"/> Yes <input type="checkbox"/> No			
10. If Yes to Item No. 9, Enter Name and Address of Reprocessor			
11. Device Available for Evaluation? (Do not send to FDA)			
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Returned to Manufacturer on: (month/year)			
12. Concomitant Medical Products and Therapy Dates (exclude treatment of event)			
E. INITIAL REPORTER			
Section E - Help			
1. Name and Address		Phone #	
2. Health Professional?		3. Occupation	
<input type="checkbox"/> Yes <input type="checkbox"/> No			
4. Initial Reporter Also Sent Report to FDA?			
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk.			

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

FORM FDA 3500A (1/09) (continued)

Section F - Help

Page 2 of _____

FDA USER ONLY

F. FOR USE BY USER FACILITY/IMPORTER (Devices Only)

1. Check One
 User Facility Importer

2. UI/Importer Report Number _____

3. User Facility or Importer Name/Address _____

4. Contact Person _____

5. Phone Number _____

6. Date User Facility or Importer Became Aware of Event (mm/dd/yyyy) _____

7. Type of Report
 Initial
 Follow-up # _____

8. Date of This Report (mm/dd/yyyy) _____

9. Approximate Age of Device _____

10. Event Problem Codes (Refer to coding manual)
 Patient Code: [] - [] - []
 Device Code: [] - [] - []

11. Report sent to FDA?
 Yes (mm/dd/yyyy) _____
 No (mm/dd/yyyy) _____

12. Location Where Event Occurred:
 Hospital Outpatient Diagnostic Facility
 Home Ambulatory Surgical Facility
 Nursing Home Outpatient Treatment Facility
 Other: _____ (Specify)

13. Report sent to Manufacturer?
 Yes (mm/dd/yyyy) _____
 No (mm/dd/yyyy) _____

14. Manufacturer Name/Address _____

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event
 Death
 Serious Injury
 Malfunction
 Other: _____

2. If Follow-up, What Type?
 Correction
 Additional Information
 Response to FDA Request
 Device Evaluation

3. Device Evaluated by Manufacturer?
 Not Returned to Manufacturer
 Yes Evaluation Summary Attached
 No (Attach page to explain why not) or provide code: _____

4. Device Manufacture Date (mm/yyyy) _____

5. Labeled for Single Use?
 Yes No

6. Evaluation Codes (Refer to coding manual)
 Method: [] - [] - [] - []
 Results: [] - [] - [] - []
 Conclusions: [] - [] - [] - []

7. If Remedial Action Initiated, Check Type
 Recall Notification
 Repair Inspection
 Replace Patient Marking
 Relabeling Modification/Adjustment
 Other: _____

8. Usage of Device
 Initial Use of Device
 Reuse
 Unknown

9. If action reported to FDA under 21 USC 3606, list correction/ remove reporting number: _____

10. Additional Manufacturer Narrative and / or

11. Corrected Date

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (not Manufacturing Site for Devices) _____

2. Phone Number _____

3. Report Source (Check all that apply)
 Foreign
 Study
 Literature
 Consumer
 Health Professional
 User Facility
 Company Representative
 Distributor
 Other: _____

4. Date Received by Manufacturer (mm/dd/yyyy) _____

5. (ANDA # _____)
 IND # _____
 OTH # _____
 PMA/ 510(k) # _____
 Combination Product Yes
 Pre-1988 Yes
 OTC Product Yes

6. If IND, Give Protocol # _____

7. Type of Report (Check all that apply)
 5-day 30-day
 7-day Periodic
 10-day Initial
 15-day Follow-up # _____

8. Manufacturer Report Number _____

9. Adverse Event Term(s) _____

The public reporting burden for this collection of information has been estimated to average 60 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 Office of Chief Information Officer
 1350 Russell Drive, 425A
 Rockville, MD 20850

OMB Statement:
 An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.