



The *REDOXS*<sup>®</sup> Study  
REducing DEaths due to OXidative STress

**A randomized trial of glutamine and antioxidant supplementation in critically ill patients**

# Serious Adverse Events

This study is registered at [Clinicaltrials.gov](http://Clinicaltrials.gov).  
Identification number NCT00133978

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## Definition of a Serious Adverse Event

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A Serious Adverse Event (experience) or reaction is any untoward medical occurrence that at any dose <sup>(1)</sup>:

- Results in death
- Is life threatening
- Requires or prolongs in-patient hospitalization
- Results in persistent or significant disability/incapacity
- May require medical or surgical intervention to prevent one of the other outcomes to defining serious

(1) Guidance for Industry, Clinical Safety Data Management Definitions and Standards for Expedited Reporting ICH Topic E2A Health Canada 1995.

### **Unexpected SAEs**

An unexpected SAE is one, the nature or severity of which is not consistent with information in the Investigators' Brochure AND fits the above definition. ***All unexpected and serious adverse events MUST be reported to Clinical Evaluation Research Unit (CERU) within 48 hrs of becoming aware of the event, regardless of the relationship of the study supplements to the event.***

### **Expected SAEs**

An expected adverse event/SAE is one that is consistent with information in the Investigators' Brochure. There are no known expected serious adverse events with the use of Dipeptiven® or Intestamin® or Micro-Se® (same components as in the REDOXS® study) mentioned in the Investigators' Brochure. Expected SAEs, including deaths, which are serious adverse events but are expected due to the progression of the underlying disease or co-morbid illnesses are NOT to be reported to CERU.

### **What should be reported to the Clinical Evaluation Research Unit (CERU)?**

***All serious (according to definition above) and unexpected*** adverse events MUST be reported to CERU, regardless of whether they are felt to be related to the study supplements (in the opinion of the PI) or not.

### ***Examples of serious and unexpected SAEs:***

*A 30 yr. patient admitted with a drug overdose develops a ST segment elevation and a myocardial infarction. This is **unexpected** and should be reported to CERU within **48 hrs** of becoming aware of this event.*

vs.

*A 65 yr old patient with a history of coronary artery disease that presents with septic shock develops positive troponin levels and ECG changes. This is **expected** and does not need to be reported to CERU.*

### ***What about unexpected death?***

***All serious events that result in unexpected death MUST be reported to CERU within 48 hrs of becoming aware of the event. For example: a patient with sepsis is improving and getting better but then dies unexpectedly the next morning. This is a serious adverse event (results in death) and was unexpected and is to be reported immediately.***

***Examples of serious and expected SAEs:***

*For example, a mechanically ventilated patient develops pneumonia. This is a serious adverse event but since pneumonia is expected, this does not need to be reported.*

NOTE: As a guideline, events that are captured in the Case Report Forms (CRFs) such as phlebitis, ICU acquired infections, dialysis, organ failures, etc are considered to be expected events and hence do not need to be captured as SAEs.

***What about expected death?***

*For example, a patient with fulminant sepsis is not improving, now has multi-organ system failure. Family has agreed to withdraw treatment and patient dies. This is a serious adverse event but death was expected due to the progression of the underlying disease (sepsis). Do not need to report to CERU.*

As with any study there may be other risks or side effects that we do not know about with administration of these study supplements. The PI must adhere closely to the ICH-GCP Guidelines, however when in doubt he/she can contact the Project Leader for the study.

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## Reporting Time Frames for SAEs

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### **Time Frames for sites to CERU**

This reporting is done in **2 phases**:

The **Serious Adverse Events Initial Report** *must* be completed and faxed to CERU **within 48 hrs** of becoming aware of each event. **This form must be completed by the PI or Study Coordinator in consultation with the PI.**

The second part of the report (**Final Report**) *must* be completed by the PI and faxed to CERU at **whatever time occurs first**:

- end of study period =day 30 (from admission to ICU)
- time of ICU d/c
- time of ICU death
- within 10 days from becoming aware of the event *if the event is fatal or life-threatening* (so that Project Leader can report to Health Canada)

### **Time Frames for CERU to Health Canada**

The Project Leader will report all serious and unexpected adverse events that are considered to be related to the study supplements to Health Canada within the time frames specified <sup>(1)</sup>:

- fatal or life-threatening SAEs:
  - immediately where possible and in any event within 7 days of becoming aware of the event
  - complete report no later than 15 days from becoming aware of the event
- non fatal/life threatening SAEs:
  - no later than 15 days from becoming aware of the event

All SAE Reports (serious and unexpected) will be forwarded to the Study Chair, the Chair of the Data Monitoring Committee (DMC), all sites and Fresenius Kabi monthly.

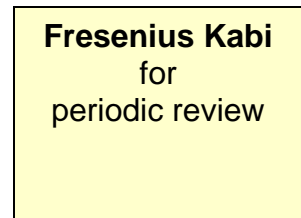
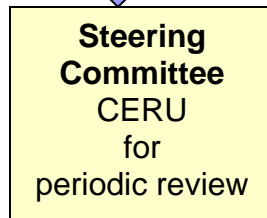
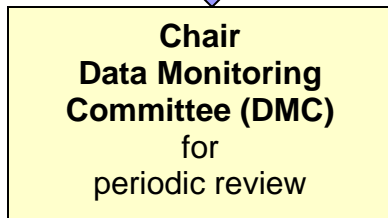
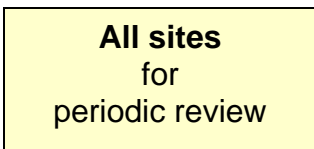
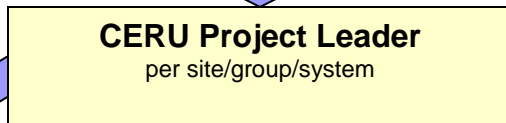
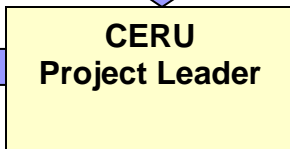
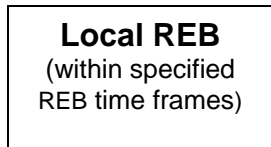
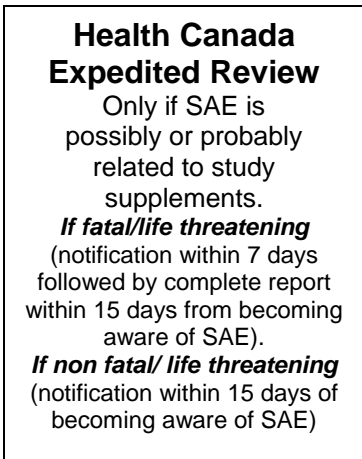
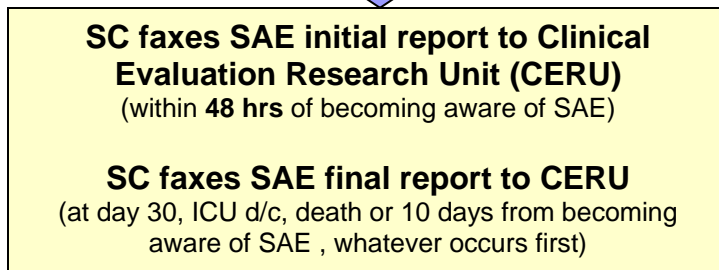
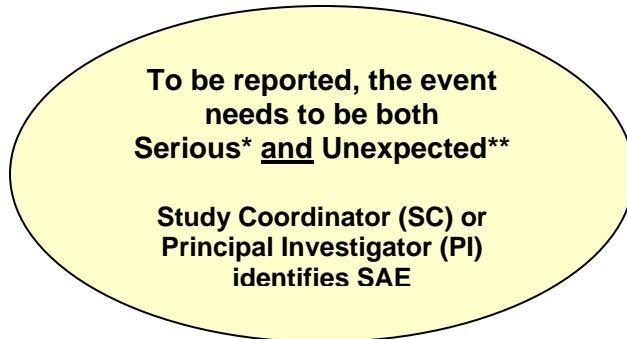
**Refer to SAE Reporting Algorithm on next page**

# SAE Reporting Algorithm

\*Serious if:

- Results in death
- Is life threatening
- Requires or prolongs in-patient hospitalization
- Results in persistent or significant disability/incapacity
- May require medical or surgical intervention to prevent one of the other outcomes to defining serious

\*\* Unexpected if:  
not expected due to the progression of the underlying disease or co-morbid illnesses.



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## SAE Report (Initial Report page 1 of 2)

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All Serious Adverse Events that are unexpected must be reported to CERU **within 48 hrs** of becoming aware of the event by filling out the **Serious Adverse Events Report (Initial Page 1 of 2) (see next page )**.

**This form must be completed by the PI or Study Coordinator in consultation with the PI and requires the signature of the PI.**

Only include those SAEs that occur during the study period. This includes the timeframe from the time of randomization to the end of the study period (actual ICU discharge, death or Study Day 30).

All known data elements on the form must be completed within 48 hrs of discovery of the event. It may be that certain aspects of the form may change (for example, the resolution date may not be known at the time of reporting) and this should be made clear in the narrative form that will follow at a later date.

For Serious Adverse Event Reported:

Do NOT record death (outcome) as a SAE but the underlying cause of death.

Do not record respiratory failure as a SAE but what was felt to cause the respiratory failure i.e. sepsis.

Once SAE form completed fax to CERU at **1-613-548-2428**

**Attention:** Project Leader REDOXS®

**Refer to SAE Report (page 1 of 2) on next page.**

This report can be downloaded off the REDOXS website under the Welcome, Home Page (Site Status Page).

**The REDOX<sup>®</sup> Study**

**Serious Adverse Events (SAE) Report**

Page 1 of 2

**Initial Report** Complete and fax to CERU at 613-548-2428 attention: Project Leader REDOX<sup>®</sup> within 48 hrs of becoming aware of 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 d/c or death, whatever occurs first).

<b>Patient Identification</b> Site # _____ Enrollment # _____ Initials _____ DOB _____ / _____ / _____ dd mmm yr <input type="checkbox"/> Male <input type="checkbox"/> Female		<b>Name of Site Investigator</b> _____ _____ _____ <b>Person reporting SAE</b> _____		<b>SAE #</b> _____ Record the sequential SAE # for this patient i.e. For 1 <sup>st</sup> SAE for this patient, write 01 For 2 <sup>nd</sup> SAE for this patient, write 02		<b>Date SAE reported</b> _____ / _____ / _____ dd mmm yr		
				<b>Date became aware of SAE</b> _____ / _____ / _____ dd mmm yr				
<b>Serious Adverse Event Reported</b> (only one per form)			<b>Seriousness (select all that apply)</b> <input type="checkbox"/> Patient died — please document date in <b>Outcomes</b> <input type="checkbox"/> Life threatening <input type="checkbox"/> Requires or prolongs hospitalization <input type="checkbox"/> Results in persistent or significant disability/incapacity <input type="checkbox"/> May require medical or surgical intervention to prevent one of the other outcomes to defining serious			<b>Outcomes (at time of initial report)</b> <input type="checkbox"/> Complete recovery/return to baseline — Date of recovery dd ___ / mmm ___ / yr ___ <input type="checkbox"/> Alive with sequelae <input type="checkbox"/> Death — death date dd ___ / ___ / mmm ___ / yr ___ <input type="checkbox"/> SAE persisting <input type="checkbox"/> Unknown/lost to follow-up		
<b>Onset of SAE</b> _____ / _____ / _____ dd mmm yr		<b>Admission to ICU</b> _____ / _____ / _____ dd mmm yr		<b>Start of Study Supplements</b> _____ / _____ / _____ dd mmm yr		<b>Resolution of SAE</b> _____ / _____ / _____ dd mmm yr		
<b>Action Taken</b> <input type="checkbox"/> None <input type="checkbox"/> Uncertain <input type="checkbox"/> Procedure or physical therapy <input type="checkbox"/> Blood or blood products <input type="checkbox"/> Prescription drug therapy <input type="checkbox"/> Non-prescription drug therapy <input type="checkbox"/> Hospitalization <input type="checkbox"/> IV fluids <input type="checkbox"/> Other, specify _____		<b>Action taken with Study Supplements</b> <input type="checkbox"/> None (including not on study supplements) <input type="checkbox"/> Dose reduced, interrupted or therapy delayed <input type="checkbox"/> Study supplements stopped permanently due to SAE		<b>Relationship of SAE to Study Supplements</b> <input type="checkbox"/> Not related <input type="checkbox"/> Unlikely related <input type="checkbox"/> Possibly related <input type="checkbox"/> Probably related		<b>Signature of Principal Investigator</b> _____ <b>Date</b> _____ / _____ / _____ dd mmm yr		

Follow up with a Final Report (on page 2) within specified timelines.

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## SAE Report (Final Report page 2 of 2)

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The **Serious Adverse Events Report (Final)** must be completed and faxed to CERU within these time frames (whatever occurs first):

- end of study period =day 30 (from admission to ICU)
- time of ICU d/c
- time of ICU death
- within 15 days from becoming aware of the event *if the event is fatal or life-threatening* (so that Project Leader can report to Health Canada)

This form **must be completed by the Principal Investigator/designate** by reviewing the Serious Adverse Events Report (Initial) and the patient's medical chart. To make this process easier, it is strongly recommended that this be done as close to the event as possible.

Since the Narrative Form will serve as the final report and will be reviewed by the Data Monitoring Committee, it **must** include details on the patients admitting diagnosis, co-morbidities, a chronological complete narration of the events leading to the SAE, the nature of the SAE, action taken with the study supplements, the outcome and the relationship to the study supplements.

The completed Narrative Form **must** be signed by the PI and faxed to CERU at:

**# 613-548-2428**

**Attention:** Project Leader, REDOXS®

**Refer to SAE Report (page 2 of 2) on next page.**

This report can be downloaded off the REDOXS website under the Welcome, Home Page (Site Status Page).

**The REDOXS® Study**  
**Final Report**

**Serious Adverse Events (SAE) Report**

page 2 of 2

Complete and fax to CERU at 613-548-2428 attention: Project Leader REDOXS at day 30, ICU d/c, death or within 10 days from becoming aware of SAE, whatever occurs first.

To be completed by Site Investigator for EVERY Initial SAE that was reported to CERU.

<b>Patient ID</b> Site # _____ Enrollment # _____ Initials _____  SAE # (from Initial Report) _____	<b>Past medical history, comorbid illnesses and reason for admission to hospital</b>	<b>Admitting diagnosis to ICU and chronological events leading to SAE</b>	<b>Chronological events preceding SAE until discharge from ICU (or day 30 or within 10 days of becoming aware of the event, whatever occurs first)</b>
<b>Confirmation of Unexpected nature of SAE</b> (not due to the progression of underlying disease)		<b>Relationship of SAE to Study supplements vs. progression of underlying illness</b> (based on timing of supplements, SAE)	<b>Outcomes (at time of final report)</b> <input type="checkbox"/> Complete recovery/return to baseline → Date of recovery dd ___/ mmm ___/yr ___ <input type="checkbox"/> Alive with sequelae <input type="checkbox"/> Death → death date dd ___/mmm ___/yr ___ <input type="checkbox"/> SAE persisting <input type="checkbox"/> Unknown/lost to follow-up
<b>Action Taken</b> <input type="checkbox"/> None <input type="checkbox"/> Uncertain <input type="checkbox"/> Procedure or physical therapy <input type="checkbox"/> Blood or blood products <input type="checkbox"/> Prescription drug therapy <input type="checkbox"/> Non-prescription drug therapy <input type="checkbox"/> Hospitalization <input type="checkbox"/> IV fluids <input type="checkbox"/> Other , specify _____	<b>Action taken with Study Supplements</b> <input type="checkbox"/> None (including not on study supplements) <input type="checkbox"/> Dose reduced, interrupted or therapy delayed <input type="checkbox"/> Study supplements stopped permanently due to SAE	<b>Summary</b>	
		<b>Relationship of SAE to Study Supplements</b> <input type="checkbox"/> Not related <input type="checkbox"/> Possibly related <input type="checkbox"/> Probably related	<b>Signature of Site Investigator</b>  _____  <b>Date</b> ___/___/___ dd mmm yy

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## SAE Monthly Tracker Form (CERU)

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- This will be completed by CERU Project Leader before the Data Monitoring Committee meetings.
- All SAEs reported will be entered on this form and will be presented per site and aggregated by group and per system.
- This form will list ALL SAEs from the start of the REDOXS® Multicentre Study.
- This SAE Monthly Tracker Form will be sent electronically to the following parties on completion:
  - All Participating Sites
  - Chair, Data Monitoring Committee (DMC)
  - Steering Committee
  - Fresenius Kabi

**Refer to SAE Monthly Tracker Form for CERU on next page.**

