



Work Instruction

WI No.: REDOX- 302-R01

Title: Serious Adverse Events Reporting: Methods Centre

Referenced SOP: Serious Adverse Event Recognition and Reporting # 302-00, Data Monitoring Committee # 407-00.

Author: Rupinder Dhaliwal, Project Leader Signature: _____ Date: _____

Intended Audience: Methods Centre

Procedures

The purpose of this work instruction is to describe the process for identifying and processing serious adverse events reported for the REDOX[®] study.

Since the patient population in the REDOX[®] study is strictly critically ill patients with organ failures that have a high baseline mortality and given the complex nature and the diversified progress of the underlying critical illness, adverse events and adverse drug reactions attributed to the natural progression of the underlying clinical condition do not need to be reported to the Methods Centre (MC). Serious adverse events must be reported if they meet the following criteria.

For the Serious Adverse Event to be reported to CERU for the REDOX[®] study, the event must be both **Serious and Unexpected**.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- 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 serious outcomes listed above

An **Unexpected Serious Adverse Event** is one, the nature or severity of which is not consistent with information in the Investigators' Brochure/Product Monograph AND fits the above definition of serious. Since there are no known expected serious adverse events in the investigator's brochure/product monograph for the REDOX investigational products, an unexpected SAE can be defined as any adverse event not attributed to the progression of the underlying disease or co-morbid illnesses.

1. All Serious Adverse Events that are unexpected must be reported by the research site to CERU within 48 hrs of becoming aware of the event, or as soon as possible.
2. The site is to do this by filling out the Serious Adverse Events Report (Initial). And faxing this to the Project Leader at 1-613-548-2428. (Appendix 1).
3. The Final Report (Appendix 2) must be completed by the site and faxed to Project Leader 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*
4. The SAE Report Form will contain, at a minimum, the following fields:
- Study Name
 - Participant ID (enrolment number, DOB, gender)
 - Name of event being reported
 - Seriousness and unexpectedness of event
 - Date/time of onset
 - Relationship to investigational product
 - Treatment for the event
 - Cause attributed to the event
 - Participant status in study
 - Outcome
5. If applicable, the research site will also report the SAE to their local Research Ethics Board (REB) using established forms and policies at the local institution.
6. Upon receipt of the SAE information, the Project Leader will review the information on the SAE report for completeness and medical coherency.
7. The Project Leader will communicate with the research site to resolve any outstanding SAE report information and to discuss any ambiguities in the information provided.
8. All SAEs must have an assessment concerning the relationship to investigational product.
Definitions will be split into four groups: not related, unlikely related, possibly related and probably related. Since the products are nutrients, there are no known events that are related. The relationship of the events to the products is based on the judgment of the Qualified Investigator. 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 "possibly related" to the investigational product.
9. The Project Leader will record all SAEs reported on to SAE Tracker (Appendix 3).
10. The Project Leader will inform the Sponsor of all reported serious and unexpected adverse events that are considered to be **possibly or probably related to the study supplements** and will report these to Health Canada according to the established time frames and procedures specified. The Project Leader will complete the *Adverse Drug Reactions (ADR) for Clinical Trials Expedited Reporting Summary Form* (Appendix 4) and fax it to Health Canada.
- a. fatal or life-threatening SAEs:
 - immediately where possible and in any event within 7 calendar days of the site becoming aware of the event.
 - complete report no later than 15 calendar days from when the site becomes aware of the event.



- b. non fatal/life threatening SAEs:
 - no later than 15 calendar days from when the site becomes aware of the event.
11. Additionally, if the SAE is considered to be possibly or probably related to the study supplements, the Project Leader will inform Fresenius Kabi. This is done to determine if there are any documented cases of the event related to the study supplements in Fresenius Kabi's records. Any relevant information will be communicated to the Data Monitoring Committee (DMC) (refer to SOP# 407: Data Monitoring Committee) and to all participating sites at the time of the SAE Summary Report submission.
12. The Project Leader will compile a SAE Summary Report from sites that will contain the following:
 - SAE Report Form (Appendix 5):
 - SAE Tracker (Appendix 3).
 - Individual SAEs reported from all sites with the DOB and initials obscured
13. The SAE Summary Report will be sent to the following parties with the Periodic Site Reports (refer to WI Site Reports):
 - DMC: for review at DMC meeting
 - All participating sites that have REB approval: for submission to their REB
 - Fresenius-Kabi: for an update.
14. The participating sites will be asked to submit the reported SAEs for all site to their REB, and to fax a copy of their REB submission or acknowledgement to the Project Leader as proof of submission. The confirmation documentation will be filed under the "Miscellaneous" section of the site binders. The confirmations will be tracked on the REB SAE Acknowledgement Log (Q:\REDOXS\Site Reports\SAE Summary Reports)
15. Refer to SAE Reporting Algorithm (Appendix 6)

Appendix 1
Serious Adverse Events Report (Initial)

The REDOX[®] Study Initial Report Complete and fax to CERU at 613-548-2428 attention: Project Leader REDOX [®] within 48 hrs of becoming aware of event.		Serious Adverse Events (SAE) Report		Page 1 of 2	
Complete one form for EVERY adverse event that is <i>Serious and Unexpected</i> . 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).					
Patient Identification Site # _____ Enrollment # _____ Initials _____ DOB _____ / _____ / _____ dd mmm yr <input type="checkbox"/> Male <input type="checkbox"/> Female		Name of Site Investigator Person reporting SAE		SAE # _____ <small>Record the sequential SAE # for this patient i.e. For 1st SAE for this patient, write 01 For 2nd SAE for this patient, write 02</small>	
				Date SAE reported _____ / _____ / _____ dd mmm yr Date became aware of SAE _____ / _____ / _____ dd mmm yr	
Serious Adverse Event Reported (only one per form)					
Seriousness (select all that apply) <input type="checkbox"/> Patient died → please document date in Outcomes <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			Outcomes (at time of initial report) <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		
Onset of SAE _____ / _____ / _____ dd mmm yr		Admission to ICU _____ / _____ / _____ dd mmm yr		Start of Study Supplements _____ / _____ / _____ dd mmm yr	
Resolution of SAE _____ / _____ / _____ dd mmm yr		Action Taken <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 _____ _____		Action taken with Study Supplements <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	
Relationship of SAE to Study Supplements <input type="checkbox"/> Not related <input type="checkbox"/> Unlikely related <input type="checkbox"/> Possibly related <input type="checkbox"/> Probably related		Signature of Principal Investigator _____ Date _____ / _____ / _____ dd mmm yr			
Follow up with a Final Report (on page 2) within specified timelines.					

Appendix 2
Serious Adverse Events Report (Final)

The REDOX[®] Study Final Report Complete and fax to CERU at 613-548-2428 attention: Project Leader REDOX [®] 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.		Serious Adverse Events (SAE) Report		page 2 of 2	
Patient ID Site # _____ Enrollment # _____ Initials _____ SAE # (from Initial Report) _____	Past medical history, comorbid illnesses and reason for admission to hospital 	Admitting diagnosis to ICU and chronological events leading to SAE 	Chronological events preceding SAE until discharge from ICU (or day 30 or within 10 days of becoming aware of the event, whatever occurs first) 		
Confirmation of Unexpected nature of SAE (not due to the progression of underlying disease) 	Relationship of SAE to Study supplements vs. progression of underlying illness (based on timing of supplements, SAE) 		Outcomes (at time of final report) <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		
Action Taken <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 _____	Action taken with Study Supplements <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	Summary 			
Relationship of SAE to Study Supplements <input type="checkbox"/> Not related <input type="checkbox"/> Possibly related <input type="checkbox"/> Probably related <input type="checkbox"/> Unlikely related		Signature of Site Investigator _____ Date ___/___/___ dd mmm yy			

Appendix 3
Serious Adverse Events Tracking and Legend

Serious Adverse Events (SAE) Tracking

SAE Case Number year/site/enrol/sequence	SERIOUSNESS (1-5)	OUTCOME (1-5)	Site Details (Investigator & Hospital)	Patient ID (initials/rand #)	EVENT	ACTION TAKEN: Other (1-9) If 9 Specify	SAE ONSET DATE (dd/mm/yyyy)	SAE RESOLUTION DATE (dd/mm/yyyy)	RELATIONSHIP: To Study Nutrients (1-3)	ACTION TAKEN: With Study Nutrients (1-3)	COMMENTS

Tracking Number Assignment:

*The SAE Case Number is assigned with a unique identifier. The number is assigned according to the following sequence: year SAE occurred, two digit site number, three digit enrollment number, and the three digit sequential number of SAE for that site. The 1st SAE occurring at site #23 for enrollment #5 on July 16, 2004 would be a SAE Case Number 200423005001

# SAEs per enrolled patients		
Site	# patients enrolled	# SAEs reported
Kingston General		
St. Joseph's Hamilton		
Ottawa General		
Ottawa Civic		
Vancouver General		
Sacre Coeur		
Maisonneuve-Rosemount		
Royal Victoria		
Royal Alexandra		

Legend for SAE Tracker

Seriousness
1 = Patient died 2 = Life Threatening 3 = Requires Hospitalization 4 = Results in persistent/significant disability 5. May require medical surgical intervention to prevent one of the outcomes defining serious
Outcome
1 = Complete recovery/Return to baseline 2 = Alive with sequelae 3 = Death 4 = Unknown/lost to Follow-up 5 = SAE persisting
Action taken
1 = None 2 = Uncertain 3 = Procedure or physical therapy 4 = Blood or blood products 5 = Prescription Drug therapy 6 = Non-Prescription Drug therapy 7 = Hospitalization 8 = IV Fluids 9 = Other (specify above)
Relationship
1 = Not Related 2 = Possibly Related 3 = Probably Related 4 = Unlikely Related
Action taken with nutrients
Study Nutrients 1 = None (including not on study nutrients) 2 = Dose reduced, interrupted or therapy delayed 3 = Study nutrients stopped permanently due to SAE

Appendix 4
Health Canada Adverse Drug Reactions (ADR) for Clinical Trials Expedited Reporting Summary Form



**Adverse Drug Reactions (ADRs) for Clinical Trials
Expedited Reporting Summary Form**

Drug Code, Generic, or Brand Name:		Sponsor of Clinical Trial:	
Report Submitted By:		(CR) File Number:	
Protocol Title / Protocol Number (if applicable):		Contact Name and Telephone Number:	
Sponsor's Identification Number for the case:		Date of ADR Onset:	
<input type="checkbox"/> Fatal or Life-Threatening Unexpected ADR <input type="checkbox"/> All other serious and unexpected ADRs		Is there an ongoing clinical trial for this drug in Canada? Yes <input type="checkbox"/> No <input type="checkbox"/>	
<small>FOR DETAILED INFORMATION ON ADVERSE DRUG REACTIONS SUBJECT TO EXPEDITED REPORTING REFER TO PART C DIVISION 5 OF THE FOOD AND DRUG REGULATIONS AND E2A 'CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING' HC / ICH GUIDELINES, 1995</small>		Is this a followup to a previous report? Yes <input type="checkbox"/> No <input type="checkbox"/>	
Reported ADR occurred in: <input type="checkbox"/> Phase I - III study <input type="checkbox"/> Phase IV study <input type="checkbox"/> Spontaneous ADR		If yes, date of previous report (s): Has the drug been or is it currently marketed in Canada? If yes, provide DIN. DIN:	
ADR Country of Origin <input type="checkbox"/> Canada <input type="checkbox"/> Other		Has the drug ever been released under the Special Access Programme/ Emergency Drug Release? Yes <input type="checkbox"/> No <input type="checkbox"/>	
		Is there a clinical trial application for this drug under review in Canada? Yes <input type="checkbox"/> No <input type="checkbox"/>	
		Is there a new drug submission for this drug under review in Canada? Yes <input type="checkbox"/> No <input type="checkbox"/>	
Signature:		ADR Reports must be provided by the following deadlines: Fatal and Life Threatening Unexpected ADRs 1. Initial Report within 7 calendar days 2. Comprehensive Report within an additional 8 calendar days	
Date:		All Other Serious and Unexpected ADRs 1. Comprehensive Report within 15 calendar days	

For Pharmaceutical Drugs: Please fax to: (613) 941-2121:
 For Biologics and Radiopharmaceuticals: Please fax to: (613) 957-0364

Adverse Drug Reaction (ADR) Expedited Reporting Summary Form (01-03)

Appendix 5
Serious Adverse Event Report

<Date>



The REDOX[®] Study
REducing Deaths due to OXidative Stress

Serious Adverse Event Report
The REDOX[®] Study (REducing Deaths due to OXidative Stress)

Duration of study	
Number of patients enrolled to date	
Number of Serious and Unexpected Adverse Events	
Number of Serious and Unexpected Adverse Events related to the study nutrients	
Number of Serious and Unexpected Adverse Events that needed expedited reporting to Health Canada	

<Comments>

cc. Data Monitoring Committee
Steering Committee
Participating sites
Fresenius-Kabi

Kingston General Hospital, Angada 4, 76 Stuart Street, Kingston, Ontario, K7L 2V7
Phone 613 549 6666 Ext. 3830 Fax 613 548 1351

Appendix 6
SAE Reporting Algorithm

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.

