



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

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

Pharmacy Manual

This study is registered at Clinicaltrials.gov.
Identification number NCT00133978

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Introduction

The Pharmacy Manual provides details on the randomization process, the storage, dispensing of study supplements and the logs to be kept by the pharmacist(s) involved in the REducing Deaths due to OXidative Stress Study (The REDOXS[®] Study).

Study Contacts

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Delegation of Authority Logs and Pharmacy Web Access Signature Log

Investigator Delegation of Authority Log

- The Pharmacist most responsible for the REDOXS[®] study procedures will sign the ***Site Investigator Delegation of Authority Log (Appendix A)***. This is to confirm that the Site Investigator has delegated the pharmacy related tasks to the most responsible pharmacist. The completed log and subsequent updates to the log is to be faxed to the Clinical Evaluation Research Unit (CERU) at (613)548-2428 by the Research Coordinator.

Pharmacy Training/Delegation Log

- In addition, the most responsible pharmacist will be responsible for further delegating tasks to the various pharmacy staff and for training. This will be done by completing the ***Pharmacy Training/Delegation of Authority Log (Appendix B)*** or a similar document. The completed log is to be faxed to the Clinical Evaluation Research Unit (CERU) at (613)548-2428 by the main pharmacist.

Pharmacy Web Access Signature Log

- The main Pharmacist(s) most responsible for the REDOXS[®] Study procedures must sign the ***Pharmacy Web Access Signature Log (Appendix C)*** provided by CERU (Clinical Evaluation Research Unit).
- Completed signature logs are to be faxed to the Project Leader at CERU at (613)548-2428 before a username and password to the web based system can be assigned.
- CERU will assign one password for each pharmacy. To maintain blinding, the password is to be changed by the main pharmacist immediately after being assigned. This password is to be shared with any site pharmacy staff involved in the preparation/checking of the dispensing.

The site Pharmacist will be responsible for notifying the CERU Project Leaders with any changes in pharmacy personnel that may have an effect on the pharmacy procedures. Updates to the Delegation Logs are to be faxed to the CERU Project Leader at (613)548-2428.

Randomization and Web Log in

The Study Coordinator will enroll a patient and this is followed by the randomization process that occurs automatically online.

The Study coordinator, who is blinded to the treatment arm, will contact the Pharmacist with the following patient details:

- patient's name
- initials
- DOB
- enrollment #
- height (in cms)

Refer to the ***Randomization Process on Web (Appendix D)*** for more details.

The Pharmacist, who will be unblinded, will **check** the treatment arm the patient is allocated to by following these steps:

1. Log on to the website for the REDOXS® study www.criticalcarenutrition.com go to REDOXS Study tab on the left hand side of the page and click on REGISTER/LOGIN or directly to https://ceru.hpcvl.queensu.ca/REDOXS_RCT
2. Enter Username
3. Enter Password (please change this password after the first time you log in).

Webshot of Log in Page

The screenshot shows a web browser window titled "REDOXS Study Login - Windows Internet Explorer". The address bar displays "https://ceru.hpcvl.queensu.ca/REDOXS_RCT/". The page content includes a header with the REDOXS logo and the text "The REDOXS® Study" and "REducing Deaths due to OXidative Stress". Below the header is a "Login page" section. On the left, there is a blue sidebar with links: "Home", "Contact Us", and "Logout". The main content area has a "Maintenance" notice in red text: "Maintenance: Please note that the Electronic data capture will be closed between 08:00 and 09:00 Eastern Standard time every Friday for regular maintenance." Below this is a "Login Existing User" section with the instruction "If you are an existing user, please enter your username and password below:". It contains two input fields labeled "User Name" and "Password", a "Forgot your password?" link, and a "Login" button.

- Click the “Login” button. If the login information is correct, you will automatically be brought to the Welcome Page that shows the treatment allocation for every patient enrolled at your site.

Webshot of Welcome Page showing Treatment Assignment

The screenshot shows the 'REDOXS Study Pharmacist View' in a Windows Internet Explorer browser. The page title is 'The REDOX[®] Study' with the tagline 'Reducing Deaths due to Oxidative Stress'. The user is logged in as 'Rupinder PharmacistLastName' at 'Site name: TEST KGH'. A table displays patient treatment assignments. A yellow callout box highlights the table with the text: 'Note: this is not the randomization list that will be used for the study.'

Site ID	Screening No	Enrolment No	Age	Height	Arm Randomized to
4	42	23	69	178.0	Antioxidants+Glutamine (AOX+GLN)
4	41	22	87	182.0	Placebo
4	39	21	43	167.0	Antioxidants (AOX)
4	38	19	56	155.0	Antioxidants (AOX)
4	37	18	43	165.0	Glutamine (GLN)
4	36	16	90	178.0	Glutamine (GLN)
4	35	15	18	250.0	Glutamine (GLN)
4	34	20	67	145.0	Antioxidants+Glutamine (AOX+GLN)
4	33	17	67	158.0	Placebo
4	32	14	178.0	Antioxidants (AOX)	
4	31	13	67	164.0	Glutamine (GLN)
4	30	12	56	176.0	Antioxidants (AOX)
4	27	11	19	160.0	Glutamine (GLN)
4	26	10	159.0	Antioxidants+Glutamine (AOX+GLN)	
4	25	9	45	187.0	Glutamine (GLN)
4	24	8	43	165.0	Placebo
4	23	7	56	165.0	Antioxidants+Glutamine (AOX+GLN)
4	22	6	55	150.0	Antioxidants (AOX)
4	21	5	123.0	Placebo	
4	18	3	78	145.0	Antioxidants+Glutamine (AOX+GLN)
4	1	4	25	188.0	Placebo
4	1	4	22.0	Placebo	

This page MUST be signed by two pharmacists to verify the randomization. Keep signed copy for your records.

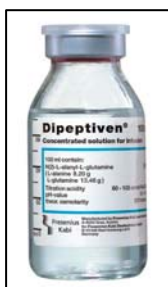
Signature of Pharmacist _____ Signature of Pharmacist _____

- This page will show the Pharmacist with 1 of 4 treatment assignments:
 - Antioxidants (AOX)
 - Glutamine (GLN)
 - Antioxidants and Glutamine (AOX+GLN)
 - Placebo
- Only these patient identifiers will be shown on the web page: Site ID, Screening #, Enrolment #, Age and Height. The Pharmacist will obtain other identifiers from the Study Coordinator (initials, DOB, CR#, etc).
- The Pharmacist must print off a copy of the randomization list (showing patient's treatment assignment) and have it signed by two pharmacists to ensure that the correct treatment arm has been noted. Please keep this signed randomization list in the pharmacy study binder.**
- Click on “Logout” button on the top left hand of the screen.

Study Supplements

THE DURATION OF THE STUDY SUPPLEMENTS SHOULD NOT EXCEED A TOTAL OF 28 DAYS.
Study supplements will be discontinued in the event that the patient is discharged from ICU or dies before 28 days (exception: patients with ICU stay < 5 days and transferred to ward; duration of study supplements should be 5 days in total).

- The enteral study supplements (EN REDOXS® formula) and the parenteral glutamine supplement (Dipeptiven) will be provided by Fresenius Kabi.
- The parenteral selenium (Selenase) will be supplied by BIOSYN.



Dipeptiven



Selenase



Enteral REDOXS formulas

For details on the Study Supplements, refer to the **Administration of Study Supplements Manual**.

Inventory of Study Supplements

- An adequate amount of both the enteral and parenteral supplements, including the parenteral selenium, will be shipped to each pharmacy by Fresenius Kabi and Biosyn, Germany before the start of the trial.
- To ensure uninterrupted enrolment to the study, the Pharmacist at each site will complete a **Monthly Site Inventory Log** (see next page) to determine the amount of supplies needed at the end of every month.
- When determining the amount of supplies needed, the Pharmacist is to consider the minimum supply needed (as specified on the Log) and the projected need for the products based on patient enrollment.
- The Pharmacist will then fax this form to the Project Assistant at CERU who will arrange for ordering the supplies. The original **Monthly Site Inventory Log** *must be kept by the pharmacist*.

URGENT Orders: Instructions for Site Pharmacists:

- Occasionally the site may have extra enrollments and suddenly require immediate product replenishment. The Pharmacist should follow the steps listed below to ensure URGENT ORDERS are addressed in a timely fashion. Please note that to maintain the study blind, contact only those persons listed below:
 1. Fill out the Monthly Inventory Log as per usual, with the number of bottles/vials indicated in the "amount needed" column.
 2. Write the word "URGENT" on the monthly inventory form, preferably on the bottom right hand corner, where it will be most visible.
 3. Fax the Monthly Inventory Form to the REDOXS Methods Centre
ATTENTION: Suzanne Biro and Susan Campbell at (613) 548-2428.
 4. Please contact Suzanne Biro (613) 549-6666 extension 6686, biros@kgh.kari.net or Susan Campbell (613) 549-6666 extension 4847, campbes3@kgh.kari.net to initiate shipping as soon as possible.

Please be advised that shipping to some sites may take two to three days. If you need study supplements sooner, it may be possible to initiate an inter-hospital transfer from a site that is geographically closer to your own.

Monthly Site Inventory Log

Month _____ Year _____

To be filled out by Site Pharmacy monthly and faxed to Clinical Evaluation Research Unit (CERU).

Name of Site: _____

Pharmacist: _____

Phone: _____

Product	Supplier	Minimum Supply needed	Actual supplies	Amount needed	Checked by CERU Project Assistant
Dipeptiven (100 ml bottles) (10 bottles per carton)	Fresenius Kabi (FK)	80 bottles*	____ bottles	____ bottles	
EN REDOX formula (500 mls bottles) (12 bottles per carton)					
AOX + GLN	FK	36 bottles ^a	____ bottles	____ bottles	
AOX	FK	36 bottles ^a	____ bottles	____ bottles	
GLN	FK	36 bottles ^a	____ bottles	____ bottles	
Placebo	FK	36 bottles ^a	____ bottles	____ bottles	
Selenase(10 ml vials)	Biosyn	40 vials ^b	____ vials	____ vials	

* based on 4 patients, each needing 2 bottles per day for 10 days

^a based on 4 patients, each needing 1 bottle per day for 9 days

^b based on 4 patients, each needing approximately 1 vials/day per day for 10 days

Signature of person completing log: _____

Date _____

Fax completed form to: CERU (613) 548-2428

Attention: REDOX[®] Study (613) 549-6666 ext 6686 or 4847

Storage of Study Supplements

- The study supplements are to be stored in the pharmacy and should be kept separate from regular stock.
- Both the enteral and parenteral products are to be stored at room temperature between 15-25°C. ***It is imperative that the temperature does not drop below 15 °C.***
- Dipectiven: once opened, is to be mixed into the other parenteral components immediately.
- Selenium: once opened, is to be used within 24 hrs if refrigerated.
- Parenteral mixtures: once the parenteral products are mixed, they are stable at room temperature (15-25 °C) for **96 hours (as per stability and compatibility studies performed on the various mixtures)**.
- Enteral products: once opened, they are to be used within 24 hours. The enteral products may show precipitation over time in the form of red or orange coloured particles floating in solution. Please shake these bottles vigorously before use. Statements from the manufacturer, Fresenius Kabi, regarding the safety and efficacy of the Enteral products with these precipitates are available from the Project Assistant. Contact the Project Assistant if you have any questions or concerns about the products.
- The pharmacist MUST keep a **temperature log** (see attached) to show that the products have been stored at the specified temperature ranges. The log is to be completed monthly and faxed to the Project Leader. These logs will be checked by the study monitor. You may use the temperature log that is currently being used at your pharmacy as long as it identifies that the products checked are related to the REDOXS[®] Study.



The REDOX[®] Study
Reducing Deaths due to Oxidative Stress

Monthly Site Temperature Log

Month _____ Year _____

To be filled out by Site Pharmacy daily and faxed to Clinical Evaluation Research Unit (CERU) monthly.

Name of Site: _____ Pharmacist: _____ Phone: _____

Date	Temperature Low Température Bas	Temperature Current Température Présent	Temperature High Température Haut	Date	Temperature Low Température Bas	Temperature Current Température Présent	Temperature High Température Haut
01				16			
02				17			
03				18			
04				19			
05				20			
06				21			
07				22			
08				23			
09				24			
10				25			
11				26			
12				27			
13				28			
14				29			
15				30			
				31			

Signature of person submitting log: _____

Fax completed form to: CERU (613) 548-2428
Attention: REDOX[®] Study (613) 549-6666 ext 6686 or 4847

Dispensing of Study Supplements

The Pharmacist at each site will be responsible for dispensing the study supplements. Hence he/she will be unblinded to the treatment assignment. To maintain blinding and to avoid a potential for bias, every attempt should be made to ensure that the Pharmacist dispensing the drugs is NOT the Pharmacist that participates in ICU rounds.

Enteral Products

1. After checking the treatment allocation online and verifying this with a second pharmacist, the primary pharmacist will obtain the appropriate enteral study supplement (as indicated on the company label AOX+GLN, AOX, GLN or Placebo).
2. The Pharmacist will then generate **two** labels for the enteral product as per template **Enteral Study Supplement Template (Appendix E)** (may be adapted to each site's needs but MUST contain all the elements shown).
3. He/she will remove the company label from the enteral bottle and place this on the **Enteral Product Label Log**, daily, and complete this form, including the date. He/she will place one of the pharmacy-generated label on the bottle.

CR# or ID# refers to the unique ID# that is assigned to each patient that is hospitalized.

4. The other label will be sent with the enteral study supplement to the ICU. The label and the enteral study supplement bottle **must** be placed together in the same bag to avoid confusion with the supplements for other patients. The bedside nurse will be instructed to place this label on the feeding bag.
5. For each patient, the Pharmacist will then record the batch # of the bottle, the expiry date and their signature on the **Enteral Study Supplement Dispensing Log**. This will be verified by a second Pharmacist. This is to be done for every patient daily.

For Study Day 1, the rate of the enteral and parenteral study supplements will likely be running at double rate to make up for the hours missed.

Depending upon the timing of the scheduled preparation for the next day, you may need to prepare an additional bag of the parenteral solution and send an additional enteral formula bottle.

Please ensure that there is enough volume prepared so that there is no interruption in the infusion of the supplements.



The REDOX[®] Study
Evaluating the effect of Oxidative stress

Enteral Product Label Log

Page ____ of ____

Pharmacist to place removable labels here daily (use one page is for 3 days)

Patient ID #: _____ Patient Initials: _____ Enrollment#: _____

Treatment Group (circle one): AOX GLN AOX+ GLN Placebo

Date dd/mm/yyyy

Date dd/mm/yyyy

Date dd/mm/yyyy



The REDOXS[®] Study
Evaluating Doxorubicin due to CM Metastases from

Enteral Study Supplement Dispensing Log Page ____ of ____

To be filled out by Pharmacist

Patient ID # _____ Patient Initials: _____ Enrollment #: _____

Dose: 480 mls/day Infusion Rate: 20 mls/hour

Treatment Group (circle one): AOX GLN AOX+ GLN Placebo

Date dd/mm/yyyy	Lot #	Expiry	Prepared by	Checked by	Checked by study monitor

For Parenteral Products

- The Pharmacist will need to prepare the parenteral solutions according to the study group the patient has been assigned to. The parenteral products will be mixed using aseptic techniques in a laminar hood flow. (See below for the study groups).

Study Groups for REDOXS®

Group	Enteral Supplement	Parenteral Supplement
AOX	AOX only	Selenium + Normal Saline
GLN	Glutamine only	Dipeptiven + Normal Saline
GLN + AOX	Glutamine + AOX	Dipeptiven + Selenium + Normal Saline
Placebo	Placebo	Placebo (Normal Saline)

- Both the parenteral supplements (Dipeptiven and Selenium) will be mixed in normal saline according to the group allocation.

The parenteral study supplements are to be mixed with saline but in the event of concerns of hypernatremia, the supplements can be mixed with D5W instead of saline. Compatibility studies of Dipeptiven and Selenium show that they are compatible with saline and D5W.

- The final parenteral solution will run at 10 mL/hour in most cases.
Exception: the patient is ≥ 196 cms tall (6 feet 5 inches) in which case the final infusion rate will need to be calculated by the Pharmacist. This rate will need to appear on the pharmacy-generated label. **(See Dosages according to Height section and Worksheets, Appendix F)**

Instructions for preparing the Parenteral Study Supplement mixture (see **Parenteral Study Supplement Worksheets for each group, Appendix F**)

- 1) Obtain patient's height (in cm) from Study Coordinator.
- 2) Determine the patient's Normal Body Weight using Broca Formula as follows:
Normal Weight (kg) = Patients height _____ cm minus 100 cm.
- 3) Determine the Volume of Dipeptiven to be given (for patients in the GLN +AOX and GLN groups). This equals:
Glutamine 0.35g/ kg/day =
L-alanyl-L-glutamine 0.5gm/kg/day =
Dipeptiven 2.5 mL/kg/day.
For patients in the AOX or Placebo group, this volume is zero.

Example:

- 1) Patient's height =170 cm and is assigned to GLN+AOX group.
- 2) Normal body weight = 170-100 = 70 kg.
- 3) Dose of Glutamine = 0.35 gm x 70 = 24.5 gm glutamine or
Dose of L-alanyl-L-glutamine = 0.5 gm x 70 = 35 gm L-alanyl-L-glutamine
or

Dose of Dipeptiven = 2.5 mL x 70 = 175 mL.

- 4) Dosage of Selenium (only for patients in the GLN +AOX and AOX groups) = 500 micrograms/day = 10 mL/day. For patients in the GLN or Placebo groups this volume is zero.
- 5) **Using an empty sterile bag, create a bag of normal saline that has exactly 250 mL (accounting for overfill). (e.g. Viaflex bag).** You may be able to bulk manufacture these bags using a compounder.
- 6) Calculate the total volume of saline to be removed from this 250 mL bag of normal saline by adding the volume of dipeptiven and selenium. This is the volume of normal saline that will need to be removed from this 250 mL bag of normal saline before adding the dipeptiven and/or selenium.
- 7) Replace the normal saline with the Dipeptiven and Selenium. The final volume of the Parenteral Study Supplement is the combination of the volumes of Dipeptiven, Selenium and normal saline and should equal to 250 mL.
- 8) Record the volume of each component dispensed (Selenium, Dipeptiven and Normal Saline) on the **Parenteral Study Supplement Dispensing Log**. The batch # and the expiry dates of all the components will be recorded daily and will be signed by the Pharmacist and co-signed by a second Pharmacist.
- 9) Any unused product(s) returned to pharmacy or expired products should be recorded on the appropriate **Nutrient Accountability Log** and should be disposed of according to your pharmacy's drug destruction policy.
- 10) The Pharmacist will then generate a label for the final parenteral product as per template titled **Parenteral Study Supplement Label (Appendix G)** (may be adapted to each site's needs but must contain the shown elements) and attach this to a normal saline bag. If the volume of the parenteral supplement is to exceed 250 mls, the correct rate will need to be calculated and should appear on the label.
- 11) Partially used vials of selenium should be refrigerated and should be used within 24 hrs for subsequent doses.
- 12) The Dipeptiven bottles can be shared between multiple patients if needed. For e.g. if one patient needs 150 mL Dipeptiven and the next patient needs 130 mL, please use 3 bottles (100 mL each) for both instead of using 4 bottles (100 mL each) for both patients. Once opened, the Dipeptiven is to be mixed into the other parenteral components immediately.

Weekend Hint: To help reduce workload on weekends, the parenteral study supplements can be dispensed ahead of time in batches of a "three-day supply" for each patient. For example, three parenteral bags can be prepared on Friday and given the expiry of 96 hours, these can be used for Saturday, Sunday and Monday (will expire Tuesday).



Page ____ of ____

To be filled out by Pharmacist

Treatment Group: (circle one): AOX GLN AOX+ GLN Placebo Infusion Rate of Final Product: 10 ml/hr (or > if tall)

[illegible]

Audited by: _____

Dosages According to Height

If the patient's height is ≥ 196 cms tall (6 feet 5 inches), the volume of the parenteral supplements increases and hence the volume of normal saline to be added decreases. Refer to ***Height and Dose of Dipeptiven (Appendix H)*** for volumes according to height.

- The final volume of the parenteral solution will be between 250 mL-300 mL. The 250 mL bag of normal saline can still be used, as it is able to hold up to 300 mL of fluid. In the event that there is no normal saline needed, you may use an empty sterile bag and add the supplements to this bag (instead of emptying an entire 250 mL bag of normal saline).
- The final rate of infusion will exceed 10 mL/hour and will need to be calculated by the Pharmacist and to appear on the pharmacy-generated label.
- Every attempt should be made to infuse the parenteral study supplements via a central line. Peripheral infusion is only recommended (for a maximum of 72 hours) in the event that there is no access to a central line.

Nutrient Accountability Log

The Pharmacist will keep track of the amount of each product dispensed (or destroyed) on the **Nutrient Accountability Log** (see next page). This log will be used by the study monitor to ensure that the patient actually received the right product.

Please note that there are a total of 6 logs, one for each of the products used (i.e. 1 each for the 4 enteral products and 1 each for the Dipeptiven and Selenium).

This will be done by cross-checking the patient enrollment #, product name and the batch # on **Nutrient Accountability Log** with the patient's initials/CR# or ID# and enrollment # on the **Dispensing Logs**.

- Record the Product Name on the Log. Use one separate log for each product i.e. Enteral products, Dipeptiven and Selenium.
- Record the date and the amount of product received (enteral products, Dipeptiven and Selenium) along with batch numbers and expiry dates.

Record the amount of product dispensed, the patient(s) enrollment # and the balance of the product remaining DAILY. Record your signature.



The REDOX[®] Study
 Reducing Toxicity due to Chemotherapy

Nutrient Accountability Log Enteral AOX

Page ___ of ___

Site #: _____

To be filled out by Pharmacist

Date	Quantity received or destroyed	Lot #	Expiry date	Quantity dispensed	Patient enrollment #	Balance of Product	Signature



The REDOX[®] Study
Evaluating the effect of Omega-3 fatty acids on

Nutrient Accountability Log Enteral GLN

Page ___ of ___

Site #: _____

To be filled out by Pharmacist

Date	Quantity received or destroyed	Lot #	Expiry date	Quantity dispensed	Patient enrollment #	Balance of Product	Signature

Audited by: _____



Page__ of __

To be filled out by Pharmacist

Audited by: _____



Page__ of __

To be filled out by Pharmacist

[illegible]

Audited by: _____



The REDOX[®] Study
Reducing Deaths due to Oxidative Stress

Nutrient Accountability Log Dipeptiven Page ___ of ___

Site #: _____

To be filled out by Pharmacist

Date	Quantity received or destroyed	Lot #	Expiry date	Quantity dispensed	Patient enrollment #	Balance of Product	Signature

Audited by: _____



The REDOX[®] Study
 Showing Benefit due to ~~CM~~ Metformin

Nutrient Accountability Log Selenase

Page ___ of ___

Site #: _____

To be filled out by Pharmacist

Date	Quantity received or destroyed	Lot #	Expiry date	Quantity dispensed	Patient enrollment #	Balance of Product	Signature

Audited by: _____

Keeping Records

The Pharmacist will keep the following signed records in addition to all other logs described in the manual above and others specified by the pharmacy.

- o Randomization record showing treatment assignment
- o Study Orders
- o Temperature Logs
- o All worksheets for each patient enrolled in the study.

These will be reviewed by an external monitor for quality assurance purposes.

Appendix A.



The REDOXS[®] Study
 Relieving Deaths due to Oesophageal Cancer

Delegation of Authority Log

This log is used by the Qualified Investigator (i.e., Site Investigator) to indicate the Site Staff that have a material effect on the conduct of the Study and to whom the Investigator has delegated significant Study related duties/tasks. The signatures and details on this log will also facilitate tracking of edits/changes of the Site records. This log is to be kept by the Qualified Investigator and the Sponsor.

Name of Qualified Investigator: _____ Signature of Qualified Investigator: _____

[illegible]

*Qualified Investigator: the Site Investigator responsible for the conduct of the REDOX[®] study at your site.

^bSub QI: Investigator other than the Qualified Investigator that is responsible for tasks related to the REDOXES® study at your site.

October 24th 2007

Reference: ICH GCP 4.1.5 and 8.3.24

1

Appendix B



Pharmacy Training/Delegation Log

This log (or a similar log) is used by the Pharmacist at each site to: 1) Indicate the pharmacy staff that have been delegated duties/tasks related to The REDOX Study and 2) Ensure that all pharmacy staff that have a material effect on The REDOX Study have been trained on the study procedures. This log (or similar log) is to be kept by the Pharmacy and sent to the Sponsor upon request.	Key Delegated Tasks 1. Maintenance of Study Product Inventory (Logs and Reorder Forms) 2. Checking of Treatment Assignment online (clinicaltrials.gov) 3. Study Product preparation and labeling 4. Maintenance of accountability logs (production, returns & destruction) 5. Checking the production of Study Product (verification of product preparation)
--	--

The participating site pharmacy at _____ has established a Standard Operating Procedure for the REDOX Study. Pharmacy personnel listed in this log have been trained according to the Standard Operating Procedures.

Name of Pharmacy contact: _____

Signature of Pharmacy Contact: _____

Print Name	Signature	Study Role (Pharmacist, Technician, etc)	Key Delegated Tasks (see above)	Training	
				Date of training	Trained by

*Pharmacy contact: is the main pharmacist/delegate that has been trained by the Methods Centre to carry out all pharmacy tasks related to the REDOX Study at the site.

Version: 16-Dec-08
Replaces version 20-Feb-08

Reference: ICH GCP 4.1.7 and 5.3.14

Appendix C



Pharmacy Web access Signature Log

INSTITUTION:
INVESTIGATOR:

SITE NUMBER:

Please complete the Electronic Data Capture (EDC) System Access Signature Sheet for each Pharmacist/technician at your site who will be checking the randomization or dispensing/checking study supplements. A signature and email address is required to create user accounts for the web based system for the REDOX[®] Study.

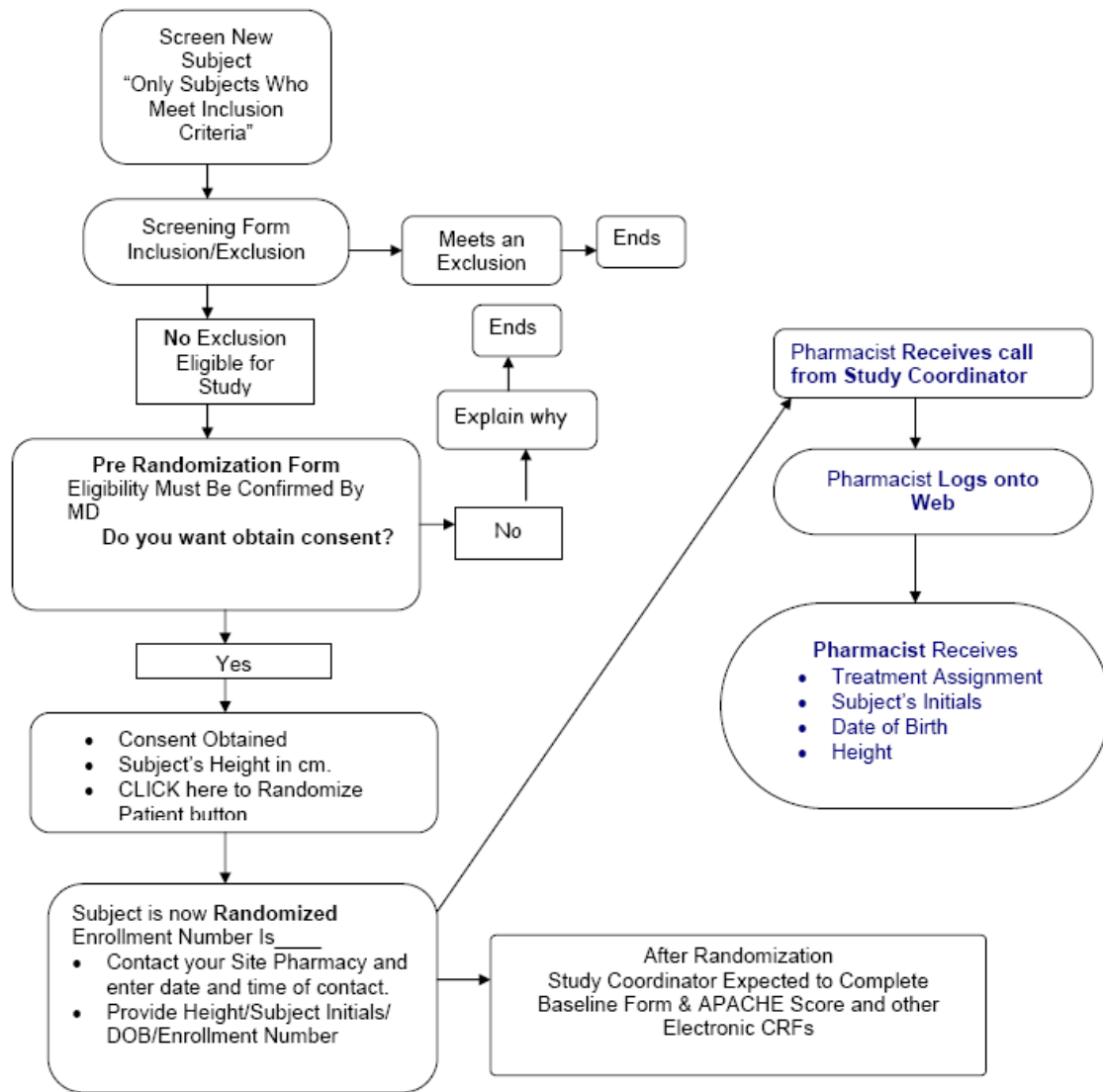
NAME	TITLE	SIGNATURE	EMAIL	DATE

NOTE:

By completing the information in the table above, the individual confirms they have been delegated the responsibility of checking the randomization and dispensing/verifying study supplements for the REDOX[®] Study.

Reference: ICH GCP 5.5.3

Appendix D Randomization Process on Web



Appendix E. Enteral Study Supplement Label Template

Enteral Study Supplement Study: REDOXS® <i>Enteral Component</i> <i>For Clinical trial Use Only</i>	
Enrollment #:	Directions:
Patient ID/CR#:	Infuse at 20 mL/hr
Patient Name:	Storage: keep between 15-25 C
Physician:	Expiry: use within 24 hours
Date:	

Appendix F. Parenteral Study Supplement Worksheets

Use the appropriate worksheet according to the group the patient has been randomized to.

These worksheets will assist in calculating the volumes of the parenteral study supplements and normal saline (or D5W) needed.

Worksheet for AOX (Antioxidant) group

Worksheet for GLN (Glutamine) group

Worksheet for GLN +AOX (Glutamine + Antioxidant) group

Worksheet for Placebo group

Parenteral Supplements Worksheet

Patient CR# / ID#	Patient Initials	Enrolment #

Antioxidants (AOX)

Patient will receive Selenium (Antioxidants) and normal saline (or if hypernatremic D5W)

Begin with a bag containing exactly 250 mL of normal saline (i.e. account for overfill):

1. Volume of Dipeptiven† to be added = 0 mL
2. Volume of Selenium to be added = 10 mL
3. Total Volume to be removed from 250 mL normal saline bag before adding study supplements:

$$\frac{\text{(# 1)}}{\text{volume of dipeptiven}} + \frac{\text{(# 2)}}{\text{volume of selenium}} = \underline{10} \text{ mL}$$

4. Add (#1) + (#2) + normal saline = 250 mL
5. Record the volumes of Selenium and Normal Saline on the Parenteral Study Supplement Log for this patient daily.
6. Generate a label and attach to bag.

†Dipeptiven not required for this treatment arm

Note: Height of the patient not required to calculate the AOX dose

Parenteral Supplements Worksheet (Patients > 196 cm tall)

Patient CR# / ID#	Patient Initials	Enrolment #

Antioxidants (AOX)

Patient will receive Selenium (Antioxidants) and normal saline (or if hypernatremic D5W)

Dosing:

1. Dosage of Selenium = 500mcg/day = 10mL/day regardless of height
2. Rate of infusion determined from chart below.
3. Dose will be diluted in a NS bag to a final volume indicated in the chart below.
4. You **must account for overfill** in the normal saline bags as per table below.

Beginning with a bag of exactly 250 mL of normal saline:

Go to height chart (see below). Record:

1. Patient height = _____ cm
2. Final total volume of the bag (from chart below) = _____ mL
3. Rate to be infused (from chart below) = _____ mL/hr
4. Volume of Selenium to be added = 10 mL

Height	Final Total Volume of Bag	Rate to be Infused	Volume of Selenium to be Added	Amount of Normal Saline	
				To be removed	To be added
196 cm	250 mL	10.4 mL/hr	10 mL	10.0 mL	
198 cm	255 mL	10.6 mL/hr	10 mL	15.0 mL	
201cm	263 mL	11.0 mL/hr	10 mL		3.0 mL
203 cm	268 mL	11.2 mL/hr	10 mL		8.0 mL
206 cm	275 mL	11.5 mL/hr	10 mL		15.0 mL
208 cm	280 mL	11.7 mL/hr	10 mL		20.0 mL
211 cm	288 mL	12.0 mL/hr	10 mL		28.0 mL
213 cm	293 mL	12.2 mL/hr	10 mL		33.0 mL

5. Volume of NS to be removed or added to bag = _____ mL
6. Add Selenium (#4), as per chart, to normal saline bag. Mix.
7. Record the volumes of Selenium and Normal Saline on the Parenteral Study Supplement Log for this patient daily.
8. Generate a label and attach to bag.

Parenteral Supplements Worksheet

Patient CR# / ID#	Patient Initials	Enrolment #

Glutamine (GLN)

Patient will receive Dipeptiven (Glutamine) and normal saline (or if hypernatremic DSW)

Begin with a bag containing exactly 250 mL of normal saline (i.e. account for overfill):

1. Patient's height = _____ cm
2. Normal Body Weight = (#1) – 100 cm = _____ kg
3. Volume of Dipeptiven† to be added = (#2) x 2.5 mL = _____ mL
4. Volume of Selenium§ to be added = 0 mL
5. Total Volume to be removed from 250 mL normal saline bag before adding study supplements:

$$\frac{\text{(\# 3)}}{\text{volume of dipeptiven}} + \frac{\text{(\# 4)}}{\text{volume of selenium}} = \text{_____ mL}$$

7. Add (#3) + (#4) + normal saline = 250 mL
8. Record the volumes of Dipeptiven and Normal Saline on the Parenteral Study Supplement Log for this patient daily.
9. Generate a label and attach to bag.

†Dipeptiven 2.5 mL/kg/day = Glutamine 0.35 g/kg/day = L-alanyl-L-glutamine 0.5 g/kg/day

§Selenium not required for this treatment arm

Parenteral Supplements Worksheet (Patients > 196 cm tall)

Patient CR# / ID#	Patient Initials	Enrolment #

Glutamine (GLN)

Patient will receive Dipeptiven (Glutamine) and normal saline (or if hypernatremic D5W)

Dosing:

1. **Dosage of Glutamine** = 0.35g/kg/day = L-alanyl-L-glutamine 0.5g/kg/day= **Dipeptivan®2.5mL/kg/day**
2. **Dosing will be based on patient's Normal Body Weight using Broca Formula as follows:**
Normal Weight (kg)= Patient's Height (cm) - 100
3. Dose will be diluted in a NS bag to a final volume indicated in the chart below.
4. **Rate of infusion determined from chart below.**
5. You **must account for overfill** in the normal saline bags as per table below.

Beginning with a bag of exactly 250 mL of normal saline:

Go to height chart (see below). Record:

1. Patient height = _____ cm
2. Final total volume of the bag (from chart below) = _____ mL
3. Rate to be infused (from chart below) = _____ mL/hr
4. Volume of Glutamine (Dipeptiven®) to be added = _____ mL

Height	Final Total Volume of Bag	Rate to be Infused	Volume of Glutamine to be Added	Amount of Normal Saline to be removed
196 cm	253 mL	10.5 mL/hr	240 mL	237 mL
198 cm	258 mL	10.8 mL/hr	245 mL	237 mL
201cm	266 mL	11.1 mL/hr	253 mL	237 mL
203 cm	271 mL	11.3 mL/hr	258 mL	237 mL
206 cm	278 mL	11.6 mL/hr	265 mL	237 mL
208 cm	283 mL	11.8 mL/hr	270 mL	237 mL
211 cm	291 mL	12.1/mL/hr	278 mL	237 mL
213 cm	296 mL	12.3 mL/hr	283 mL	237 mL

5. Volume of NS to be removed from bag = _____ mL
6. Add Dipeptiven® (#4), as per chart, to normal saline bag. Mix.
7. Expiry dating = 96 hours at room temperature.
8. Generate a label and attach to bag.

Parenteral Supplements Worksheet

Patient CR# / ID#	Patient Initials	Enrolment #

Antioxidants + Glutamine (AOX+GLN)

Patient will receive Selenium (AOX), Dipeptiven (GLN) and normal saline (or if hypernatremic DSW)

Begin with a bag containing exactly 250 mL of normal saline (i.e. account for overfill):

1. Patient's height = _____ cm
2. Normal Body Weight = (#1) – 100 cm = _____ kg
3. Volume of Dipeptiven† to be added = (#2) x 2.5 mL = _____ mL
4. Volume of Selenium to be added = 10 mL
5. Total Volume to be removed from 250 mL normal saline bag before adding study supplements:

$$\frac{\text{(#3)}}{\text{volume of dipeptiven}} + \frac{\text{(#4)}}{\text{volume of selenium}} = \text{_____ mL}$$

6. Add (#3) + (#4) + normal saline = 250 mL
7. Record the volumes of Dipeptiven, Selenium and Normal Saline on the Parenteral Study Supplement Log for this patient daily.
8. Generate a label and attach to bag.

†Dipeptiven 2.5 mL/kg/day = Glutamine 0.35 g/kg/day = L-alanyl-L-glutamine 0.5 g/kg/day

Parenteral Supplements Worksheet (Patients > 196 cm tall)

Patient CR# / ID#	Patient Initials	Enrolment #

normal Saline on the Parenteral Study Supplement Log for this

Antioxidants + Glutamine (AOX+GLN)

Patient will receive Selenium (AOX), Dipeptiven (GLN) and normal saline (or if hypernatremic D5W)

Dosing:

1. **Dosage of Selenium** = 500mcg/day = 10mL/day regardless of height;
2. **Dosage of Glutamine** 0.35g/kg/day = L-alanyl-L-glutamine 0.5g/kg/day= **Dipeptivan®2.5mL/kg/day**
3. Dosing will be based on patient's Normal Body Weight using Broca Formula as follows: Normal Weight (kg) = Patient's Height(cm) - 100
4. Dose will be diluted in a NS bag to a final volume indicated in the chart below.
5. **Rate of infusion determined from chart below.** (rate may be increased up to 2x the amount on day 1 for hours missed to conform to standard dosing times)
6. You **must account for overfill** in the normal saline bags as per table below.

Beginning with a bag of exactly 250 mL of normal saline:

Go to height chart (see below). Record:

1. Patient height = _____ cm
2. Final total volume of the bag (from chart below) = _____ mL
3. Rate to be infused (from chart below) = _____ mL/hr
4. Volume of Selenium to be added = 10.0 mL
5. Volume of Glutamine (Dipeptiven®) to be added = _____ mL

Height	Final Total Volume of Bag	Rate to be Infused	Volume of Selenium to be Added	Volume of Glutamine to be Added
196 cm	250 ml	10.4 mL/hr	10 mL	240 mL
198 cm	255 ml	10.6 mL/hr	10 mL	245 mL
201cm	263 ml	11.0 mL/hr	10 mL	253 mL
203 cm	268 ml	11.2 mL/hr	10 mL	258 mL
206 cm	275 ml	11.5 mL/hr	10 mL	265 mL
208 cm	280 ml	11.7 mL/hr	10 mL	270 mL
211 cm	288 ml	12.0 mL/hr	10 mL	278 mL
213 cm	293 ml	12.2 mL/hr	10 mL	283 mL

6. Begin with an empty sterile bag, draw up: Selenium (#4) and Glutamine (#5). Add to the bag and mix.
7. Expiry dating = 96 hours at room temperature.
8. Generate a label and attach to bag.

Parenteral Supplements Worksheet

Patient CR# / ID#	Patient Initials	Enrolment #

Placebo Patient will only receive normal saline (or if hypernatremic D5W)

Begin with a bag containing exactly 250 mL of normal saline (i.e. account for overfill):

1. Volume of Dipeptiven† to be added = 0 mL
2. Volume of Selenium§ to be added = 0 mL
3. No mixing needed. The patient will receive a 250 mL bag of normal saline.
4. Record the volume of Normal Saline (=250 mL) on the Parenteral Study Supplement Log, for this patient daily.
5. Generate a label and attach to bag.

†§Dipeptiven and Selenium not required for this treatment arm.

Patient CR# / ID#	Patient Initials	Enrolment #

Parenteral Supplements Worksheet (Patients > 196 cm tall)

I Dipeptiven on the Parenteral Study Supplement Log for this

Placebo Patient will only receive normal saline (or if hypernatremic D5W)

Dosing:

1. Dose will consist of a 250mL NS bag with added NS to a final volume as indicated in chart below.
2. **Rate of infusion determined from chart below**

Beginning with a bag of exactly 250 mL of normal saline:

Go to height chart (see below). Record:

1. Patient height = _____ cm
2. Final total volume of the bag (from chart below) = _____ mL
3. Rate to be infused (from chart below) = _____ mL/hr
4. Volume of normal saline to be added = _____ mL

Height	Final total volume of bag	Rate to be infused	Amount of normal saline to be added
196 cm	250 mL	10.4 mL/hr	
198 cm	255 mL	10.6 mL/hr	5 mL
201 cm	263 mL	11.0 mL/hr	13 mL
203 cm	268 mL	11.2 mL/hr	18 mL
206 cm	275 mL	11.5 mL/hr	25 mL
208 cm	280 mL	11.7 mL/hr	30 mL
211 cm	288 mL	12.0 mL/hr	38 mL
213 cm	293 mL	12.2 mL/hr	43 mL

5. Record the volume of Normal Saline (as per final volume on chart above) on the Parenteral Study Supplement Log, for this patient daily.
6. Generate a label and attach to the bag.

Appendix G. Parenteral Study Supplement Label Template

Parenteral Study Supplement	
Study: REDOXS®	
<i>Parenteral Component</i>	
<i>For Clinical trial Use Only</i>	
Enrollment #:	Directions:
Patient CR#/ID#:	Infuse at 10 mL/hr
Patient Name:	Storage: keep between 15-25C
	Expiry:
Physician:	
Date:	

Appendix H. Height and Dose of Dipeptiven

Ht (ft in)	Ht (cms)	Dipeptiven mls	Se mls	N/S mls	Total mls
6'0"	183	208	10	32	250
6'1"	185	212	10	28	250
6'2"	188	220	10	20	250
6'3"	191	228	10	12	250
6'4"	193	233	10	7	250
6'5"	196	240	10	---	250
6'6"	198	245	10	---	255
6'7"	201	253	10	---	263
6'8"	203	258	10	---	268
6'9"	206	265	10	---	275
6'10"	208	270	10	---	280
6'11"	211	278	10	---	288
7'0"	213	283	10	---	293