



Work Instruction

WI No.: REDOXS- 206-R01

Title: Generation and Distribution of Agreements

Referenced SOP: Generation and Distribution of Agreements # 206-01

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

Intended Audience: Methods Centre

Procedures

The purpose of this work instruction is to outline the process for preparation, review and distribution of site agreements between the methods centre (MC) and research sites participating in the REDOX[®] study.

All research sites participating in the REDOX[®] Study must have a fully executed site agreement in place prior to recruitment of study participants.

1. A generic site agreement will be developed by the legal counsel at the Office of Research Services (ORS) at Queen's University. The agreement should include the details outlined in the SOP # 206-01 at a minimum and will be approved by the Sponsor. ORS will be responsible for ensuring that the legal requirements are included in the agreement.
2. Prior to the start of the study, the Project Leader at the MC in conjunction with the Sponsor, will adapt the generic site agreement to create a template that is specific to the REDOX[®] study (see appendix 1). The template may be adapted further to reflect the specific needs of certain sites pertaining to insurance, indemnification, budget, etc.
3. The Project Leader will forward the site specific agreement template to the research site. The site will review the agreement and forward it to their contracts office for further review and inclusion of site specific details around names of individuals involved. The site agreement template will be sent to the research site as part of the start-up documents or may be sent separately.
4. The Project Leader will ask that any negotiations/comments/questions regarding the agreement be copied to him/her and be sent to the contact persons at ORS:
5. Communication will continue between the Project Leader, ORS and the research site until all outstanding issues are resolved and both parties are prepared to finalize the agreement. The Project Leader will involve the Sponsor as needed and will facilitate the communication between all parties in order to avoid unnecessary delays in the execution of the agreement.
6. ORS will distribute enough originals of the finalized agreement to all parties for signatures. If the Project Leader receives the agreement before ORS, this will be forwarded to ORS for distribution.
7. The Project Leader will ask ORS for a periodic update on the status of agreements that are pending.



8. Once the agreement is fully executed (i.e. fully signed), the Project Leader will file a copy in the CERU Site specific Binder under Site Agreements. The research site will be instructed to maintain a copy as per their institutional policies. ORS will also file one copy as per their policies.



Appendix 1. Template of Site Agreement for The REDOX[®] Study

SITE AGREEMENT

This agreement is made as of _____, 2008, by and between

QUEEN'S UNIVERSITY AT KINGSTON

And

THE BOARD OF GOVERNORS OF THE KINGSTON HOSPITAL,
COMMONLY KNOWN AS KINGSTON GENERAL HOSPITAL
(collectively referred to as "Institution")

and

DR. DAREN HEYLAND

(the "Principal Investigator")

and

<<insert name of institution>>
(the "Site")

and

DR. << insert name >>

(the "Site Investigator")

BACKGROUND:

- A. The Principal Investigator has designed the clinical trial ("Clinical Trial") as set out in the protocol entitled "**A Randomized Trial of Glutamine and Antioxidant Supplementation in Critically Ill Patients: The REDOX Study**".
- B. This Clinical Trial is supported by funding granted to the Principal Investigator and the Institution from the Canadian Institutes of Health Research. Fresenius Kabi Deutschland GmbH (FK) will provide the products under investigation in this Clinical Trial (the "Investigative Material(s)").
- C. The Clinical Trial will be performed as part of a multi-centre initiative. The Principal Investigator will act as the Sponsor-Investigator for the Clinical Trial



D. The Institution and the Principal Investigator wish the Site Investigator and Site to participate in the Clinical Trial to be conducted at the Site.

E. The Site Investigator and Site wish to conduct and take part in the Clinical Trial.

THE PARTIES THEREFORE AGREE AS FOLLOWS:

1. CONDUCT OF THE CLINICAL TRIAL

1.1 The Site Investigator and Site shall perform the Clinical Trial and shall ensure that all support staff perform their assigned duties with respect to the conduct of the Clinical Trial strictly in accordance with the standards, procedures and policies set out in the protocol entitled “**A Randomized Trial of Glutamine and Antioxidant Supplementation in Critically Ill Patients: The REDOX Study**” as attached as Appendix A to this Agreement, or as hereinafter revised, (“Protocol”). However, neither the Site Investigator nor Site promises success in achieving any particular results. Except as expressly provided in this Agreement, the Site Investigator and Site give no warranty, express or implied, as to any matter, including, without limitation, as to the results of the Study.

1.2 The Clinical Trial shall be carried out under the direction and supervision of the Site Investigator who shall have responsibility for the scientific and technical conduct of the Clinical Trial at the Site. The Site Investigator shall be responsible for ensuring that all staff and hospital personnel are properly informed of and perform their assigned duties with respect to the Clinical Trial strictly in accordance with the procedures and policies specified in the Protocol, and the confidentiality requirements as per section 3 found below.

1.3 The Site will provide all necessary equipment, personnel and any support necessary to commence and complete the Clinical Trial.

1.4 Each party shall ensure that all work it carries out under the Clinical Trial complies with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ICH/GCP), the Tri-Council Guidelines, the customary principles of ethical research, and all other applicable laws and regulations including but not limited to obtaining and documenting the written informed consent of all research subjects recruited to the Clinical Trial in accordance with the Protocol. The Parties will in addition ensure that the Clinical Trial is conducted in compliance with established ethical standards, as reflected in ICH/GCP and the Declaration of Helsinki.

1.5 The Site Investigator shall provide to the Principal Investigator the Site’s Research Ethics Board approval letter of the Protocol before the Clinical Trial may commence at the Site.

1.6 The Site Investigator will forward a copy to the Principal Investigator of all serious adverse events according to the process defined by the Principal Investigator. The Principal Investigator will forthwith report all serious and/or unexpected adverse events as defined in the ICH/GCP Guideline or as required by applicable regulations to the appropriate regulatory authorities including the Therapeutic Products Directorate of Health Canada (TPD) and the Site



Investigator and/or Site shall receive a copy of the report. At the request of Site and/or the Site Investigator, the Principal Investigator will report within the applicable time-lines to all regulatory agencies in the jurisdictions in which the Clinical Trial is taking place all serious adverse events which in the Site Investigator's sole discretion may be related to the Investigative Material(s), and, therefore, warrant such reporting, failing which the Site and the Site Investigator shall be entitled to make such reporting.

1.7 The Protocol allows for electronic data capture and management. The Site and Site Investigator therefore agree to comply with the "Additional Responsibilities" attached as Appendix C.

2. PUBLICATION

2.1 Site Investigator and Site agree that the first presentation or publication of the results of the Clinical Trial at the Site shall be made in conjunction with the publication of the results from all site investigators and sites participating in the Clinical Trial. Authorship of the initial publications of results shall be decided by the Steering Committee (as defined in the Protocol), in accordance with the criteria for authorship as formulated by the International Committee of Medical Editors and published in its *Uniform Requirements for Manuscripts submitted to Biomedical Journals* (NEJM 336(4):309-316, January 23, 1997). The Steering Committee's objective is to disseminate the results of the Clinical Trial within a reasonable period, free from censorship or editorial rights of the source of funding.

2.2. If no multi-center publication has commenced within 12 months after the close of the Clinical Trial at all sites, Site Investigator is free to present or publish the results from the Site in accordance with the clause herein. The Site Investigator will forward a copy of any such presentation or manuscript for publication to the Principal Investigator for review and comment at least 30 days before presentation or publication. The Site Investigator acknowledges that a copy of the manuscript will be forwarded by Principal Investigator to FK. No Confidential Information of FK will be included in any presentation or manuscript without the written consent of Institution or FK, provided that it is acknowledged that site specific study results shall not constitute FK confidential information for the purposes of publication pursuant to this Section 2.

2.3 Institution, Principal Investigator and Site will be acknowledged for their contribution to the publication.

3. CONFIDENTIALITY

3.1 Prior to or during the course of the Clinical Trial, Institution or Principal Investigator may provide Site Investigator or the Site with information related to the Clinical Trial or the Investigative Material(s) (the "Confidential Information"). The Confidential Information will not be disclosed by Site Investigator or the Site without the prior written approval of the Principal Investigator. This obligation of confidentiality shall survive the completion or early termination of the Study for a period of five (5) years; provided, however, the obligation of confidentiality



for any Confidential Information clearly marked as Confidential Information of FK shall survive for an indefinite period, subject only to the exceptions set out in section 3.2 below. Site Investigator or the Site may from time to time disclose Confidential Information to support staff involved in the Clinical Trial, and Site's Research Ethics Board but only to the extent required for the proper conduct of the Study and provided that each member of the support staff and each Research Ethics Board to whom disclosure is made is fully informed of the confidential nature of the information disclosed and agrees to keep it confidential in accordance with this Agreement. Site Investigator and the Site shall keep accurate and complete records of disclosures of Confidential Information to support staff and Research Ethics Board and shall ensure that all copies of Confidential Information are returned to the Principal Investigator or destroyed at the Principal Investigator's request.

3.2 The obligations of confidentiality set out in section three herein shall not apply to Confidential Information which,

(a) can be shown by Site Investigator or the Site to have been in Site Investigator's or Site's possession before any disclosure hereunder or in relation to this Clinical Trial;

(b) at time of disclosure is, or thereafter becomes, without breach of this Agreement, part of the public domain by publication or otherwise;

(c) is lawfully furnished to Site Investigator or the Site by a third party who has no obligation of confidentiality to Institution, Principal Investigator, or to FK or its affiliates with respect to such information;

(d) must be disclosed to potential patients during the recruitment process, and patients who are or were enrolled in the Study, or any of their lawful representatives, in order to obtain and maintain informed consent or as the information relates to their health, safety or diagnosis;

(e) is independently developed by employees, agents or consultants of Site and/or Site Investigator who had no knowledge of or access to information obtained from Institution, Principal Investigator or from FK;

(f) is required by statute or judicial process to be disclosed in which case Site and Site Investigator shall notify Institution and Principal Investigator of such disclosure and provide Institution and Principal Investigator with an opportunity to comment on such proposed disclosure. Site Investigator and/or the Site will disclose only that portion of said information which it is legally required to disclose.

4. INTELLECTUAL PROPERTY RIGHTS

4.1 Data and results from the Clinical Trial shall be the property of Principal Investigator and Institution. The data will be stored at the Institution. Requests for access to data resulting from this Agreement may be made to Principal Investigator. Site may retain a copy of the data only for archival purposes and subject to the confidentiality provisions.

4.2 Title to any inventions or discoveries arising from this Clinical Trial and conceived or reduced to practice by Site or Site Investigator shall be owned by Site or Site Investigator (in



accordance with its intellectual property policies) and shall be promptly disclosed in writing to Institution and Principal Investigator. Principal Investigator shall forward a copy of any such disclosure to FK. Site and Site Investigator acknowledge that FK will be allowed access to the results of the Clinical Trial, including all data, inventions, or discoveries, but subject always to applicable patient privacy laws and regulations. No patient records will leave the Site. .

5. LIABILITY

5.1 The parties covenant and agree that:

- (a) Each party shall assume its/his/her own liability for any costs, suits or claims on account of injuries (including death) to persons or damage to property to the extent that such injuries or damage arise out of its/his/her activities in the course of or arising out of the Clinical Trial or the activities of those for whom in law it/he/she is responsible;
- (b) No party or its/his/her trustees, directors, officers, employees, and agents (the 'first party') shall be liable to any other party (the 'second party') for any costs claimed, or suits or claims made by the second party or made against the second party except to the extent caused by negligence or willful misconduct on the part of the first party; and,
- (c) No party shall be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by another party.

5.2 The parties hereto agree that they shall cooperate with each other in the defense of any such action, including providing each other with prompt notice of any such action and provision of all material documentations. The parties further agree that they have a right to retain their own counsel to conduct a full defense of any such action.

6. INSURANCE

6.1 Institution and Site each with respect to itself represent and warrant that they have sufficient commercial general liability insurance coverage and healthcare liability insurance or self-insurance coverage to cover their respective obligations under this Agreement.

6.2 The Principal Investigator and Site Investigator each individually represent and warrant that they have membership in the Canadian Medical Protective Association (CMPA) and will maintain such membership or otherwise maintain sufficient medical professional and/or medical malpractice liability insurance during the term of this Agreement and shall provide evidence of such insurance to the other parties upon request. .

7. NOTICES



Any demand, notice or other communication in connection with this Agreement shall be given in writing and shall be given by personal delivery (in which case it shall be left with a responsible officer of the recipient) or by electronic communication addressed to the recipient as follows:

To INSTITUTION:

Director, Research Services

TEL:

FAX:

With A Copy To: _____
Vice President Research Development

TEL:

FAX:

To PRINCIPAL INVESTIGATOR:

Dr. Daren Heyland
Kingston General Hospital
76 Stuart Street
Kingston ON K7L 2V7

TEL:

FAX:

To SITE:

<<insert contact name and title>>

<<insert address>>

<< insert phone and fax>>

To SITE INVESTIGATOR:

<<insert name>>

<<insert address>>

<<insert phone and fax>>

8. PAYMENT

8.1 Payments will be made in accordance with the schedule of payment attached as Appendix B. Payments are made on a per patient enrollment basis and once the completed Case Report Forms are received by the INSTITUTION.

8.2 It is anticipated that 2 to 3 patients per month will be enrolled in the Clinical Trial at the Site. Patient enrolment will commence in _____ 2008.

8.3 All cheques should be made payable to:

<<insert name of hospital>>

c/o Dr. << insert name>>

<<insert address>>



9. PATIENT CONFIDENTIALITY

All parties will abide by all applicable privacy legislation including the *Personal Health Information Protection Act* (PHIPA) as it pertains to use, disclosure and collecting of personal health information.

10. DATA COLLECTION

Site Investigator and Site shall ensure that the data collected are kept as required by the applicable laws, rules and regulations including but not limited to Health Canada requirements.

11. MONITORING AND QUALITY ASSURANCE AUDIT

11.1 Principal Investigator and Institution reserve the right, subject to Section 9 of this Agreement, to monitor the Clinical Trial through their own clinical monitors who will be given access to all information resulting from the Clinical Trial in order to comply with regulatory requirements. The monitor(s) shall have access to laboratory test reports and other patient/subject records needed to verify the entries on the case report forms.

11.2 Principal Investigator and Institution reserve the right to audit the Clinical Trial or have the Clinical Trial audited by a designee to document the authenticity of recorded data and Protocol adherence. Any such audits shall occur at mutually agreeable times during normal business hours. Patients/subjects participating in the Clinical Trial shall be informed by Site Investigator or Site that their records may be reviewed for this purpose, including by government health authorities. The confidentiality of such patient records will be respected fully as required by law.

12. ASSIGNMENT

No part of this Agreement may be assigned, delegated, or subcontracted by any party to any other person or third party without the prior written approval of all parties.

13. TERMS AND TERMINATION

This Agreement may be terminated by any party, (i) upon a breach of the terms of this Agreement by another party if such breach is not remedied within 30 days of receipt of notice thereof; (ii) in the event of recall of any Investigative Material(s) for any reason; (iii) upon 60 days prior written notice; or (iv) immediately if deemed necessary by that party for patient safety concerns. If the Agreement is terminated all costs properly incurred in the conduct of the Clinical Trial pursuant to the budget, up to the point at which it was terminated, will be reimbursed to the Site at the next payment date according to Exhibit B.

14. ENTIRE AGREEMENT

This Agreement represents the entire understanding of the parties with respect to the subject matter hereof. In the event of any inconsistency between this agreement and the Protocol, the terms of this Agreement shall govern. Subject to the limitations otherwise expressed herein, this Agreement shall enure to the benefit of and be binding upon the parties, and their respective successors and permitted assignees.

15. SEVERABILITY



The invalidity or unenforceability of any term or provision of this Agreement shall not affect the validity or enforceability of any other term or provision hereof.

16. WAIVER

No waiver of any term, provision or condition of this Agreement whether by conduct or otherwise in any one or more instances shall be deemed to be construed as a further or continuing waiver of any such term, provision or condition of this Agreement.

17. AMENDMENT

This Agreement can only be amended if the amendment is signed by all parties.

18. INTEGRATION

The Protocol marked as Appendix A; Payment Schedule marked as Appendix B; and Additional Responsibilities marked as Appendix C are incorporated into this Agreement.

19. FORCE MAJEURE

No Party shall be responsible to the others for any delay in the performance of, or failure to perform, this Agreement where such delay or failure is caused by circumstances beyond the reasonable control of the affected Party including, without limitation, strikes, lockouts or any other labour disruptions, war, civil commotion, natural disaster, disease or epidemics, or acts of God. In the event of any such delay or failure in performance, the affected party shall be granted an extension of time for performance that is equitable in light of the cause of the delay.

20. RELATIONSHIP OF PARTIES

The parties hereto are independent contractors. Nothing contained herein shall be deemed or construed to create between the parties hereto a partnership or joint venture or employment relationship. No party shall have the authority to act on behalf of any other party or to bind another party in any manner.

21. SURVIVAL OF TERMS

Sections 2, 3, 4, 5, 6, 9, 10 and this section 21 shall survive any termination or expiration of this Agreement, as well as any other terms which by their intent or meaning are intended to survive. No termination hereunder shall constitute a waiver of any rights or causes of action that any party may have based upon events occurring prior to the termination date.

22. GOVERNING LAW

The parties agree that this Agreement shall be governed by the laws of the Province of Ontario and the laws of Canada, as applicable, without regard to conflict of law rules, and hereby attorn to the jurisdiction of the courts of the Province of Ontario.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed by their duly authorized representatives as of the date first above written.

INSTITUTION

Queen's University at Kingston



By: _____
Director, Research Services

Date

**The Board of Governors of the Kingston Hospital,
commonly known as Kingston General Hospital**

By: _____
Vice President Research Development

Date

PRINCIPAL INVESTIGATOR

Dr. Daren Heyland

Date

SITE

By: <<Insert Name>>
<<insert title>>
<<insert Institution>>

Date

SITE INVESTIGATOR

<<insert name>>

Date



APPENDIX A

Protocol

Previously provided.



APPENDIX B

Payment Schedule

Payments will be made on the following basis:

- \$_____ CDN for each completed, eligible, randomized subject (inclusive of all costs, including any overhead/indirect cost, pharmacy fees, and other direct costs.)
- \$_____ CDN for each quality of life questionnaire properly completed at 3 and 6 months.
- For any subject who remains in the study for less than five days, the payment will be \$_____ CDN.

Schedule of Payments

1. Institution will advance an initial payment of \$_____ CDN on request following research ethics board approval and execution of this agreement.
2. Remaining payments will be made quarterly based on the number of satisfactorily completed case records received at the Institution.
3. Enrollment is competitive; therefore, once the overall maximum number of subjects has been reached, each Site will be given notice by Principal Investigator that enrollment into the Clinical Trial is closed.



APPENDIX C Additional Responsibilities

- Site shall supply its own computer with internet access and will be responsible for the maintenance of its own computing equipment.
- Site Investigator will collect screening data on enrolled and excluded patients and enrolled patient data on a daily basis using the Web Electronic Data Capture System .
- Site Investigator shall notify Principal Investigator of any technical difficulties or malfunctions related to the Web Based System.
- Site Investigator will ensure only authorized clinical site study personnel with assigned password access to the web based system (as specified on the signature sheet provided) will complete electronic data capture for the Study.
- Site Investigator shall have personnel complete protocol Violation Forms within 24 hours of identification.
- Site Investigator shall ensure Principal Investigator is notified within 48 hours of identification of a Serious Adverse Event.
- Site Investigator will respond to data queries from Principal Investigator within 7 working days.
- Site Investigator shall complete all data within 2 months of randomization. Exceptions will be the Hospital Outcome Form (if patient still in hospital after Day 28), and the quality of life questionnaires (at 3 and 6 months).
- Site and Site Investigator will accommodate site visits by Institution personnel at mutually agreeable dates and times.
- Clinical Sites and/or Site Investigator will notify the Principal Investigator of any changes in personnel and/or contact information.