CONFIDENTIAL DOCUMENT

Clinical Trial Protocol

Title:

STudy to ActivelY WARM Trauma Patients – 2 (STAYWARM-2): A pilot feasibility trial of chemical versus passive warming blankets in massively bleeding patients

Protocol Number:
v2.5 2023-08-21

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Funding Agency	Sunnybrook Practice Based Research and Innovation (PBRI)
Investigational Product	ReadyHeat Blanket

PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant, and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the REB approved protocol, GCP and applicable regulatory requirements, including confidentiality, ethical guidelines and regulations regarding the conduct of research in humans.

Qualified Investigator:

Name: *(Print)*	Luis Da Luz
Title & Institution: *(Print)*	Principal Investigator, Sunnybrook Health Sciences Centre
Signature:	
Date of signature: *(yyyy-mmm-dd)*	

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LIST OF ABBREVIATIONS

The following abbreviations describe terms, documents and study personnel used in the conduct of this study protocol.

AE	Adverse Event
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Case Report Forms
DSMB	Data And Safety Monitoring Board
ED	Emergency Department
FAWB	Forced Air Warming Blanket
GCP	Good Clinical Practice Guidelines
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
INR	International Normalized Ratio
MHP	Mass Hemorrhage Protocol
MRP	Most Responsible Provider
OR	Operating Room
PHI	Personal Health Information
PHIPA	Personal Health Information Protection Act Of 2004
RCT	Randomized Control Trial
SAE	*Serious Adverse Event*
SD	Standard Deviation
SHSC	Sunnybrook Health Sciences Center
SUADR	Serious Unexpected Adverse Drug Reactions
TDL	Task Delegation Log

PROTOCOL SUMMARY

PRINCIPAL INVESTIGATOR	Luis Da Luz MSc MD
PROTOCOL TITLE	STudy to ActivelY WARM Trauma Patients – 2 (STAYWARM-2): A pilot feasibility trial of chemical versus passive warming blankets in massively bleeding patients
PROTOCOL NUMBER	
PHASE	I
INVESTIGATIONAL PRODUCT AND PLANNED USE	To evaluate the (1) Feasibility of the Ready-Heat® blanket to increase temperature by at least 1^{o}C at eight hours from arrival to the trauma bay in severely injured trauma patients to whom a massive hemorrhage protocol is activated; (2) Feasibility of adherence to the application of the Ready-Heat® blanket in patients enrolled in the intervention arm throughout the trauma bay resuscitation; (3) Feasibility of adherence to body temperature measurement throughout the different phases of care (i.e.: TB, ED, CT scanner suite, OR, IR suite, ICU) ; (4) Feasibility of maintenance of at least one Ready-Heat® blanket applied throughout the different phases of care (i.e.: TB, ED, CT scanner suite, OR, IR suite, ICU)
STUDY DESIGN	A phase I, single center, pilot, feasibility, prospective, open-label RCT
DURATION OF FOLLOW-UP	From first application of study product to final study visit = 8 hours
TREATMENT ALLOCATIONS	Experimental arm: 2 Ready-Heat® 4-panel blankets Control arm: standard of care (use of warmed blankets and forced air warmed blanket [FAWB])
PATIENT POPULATION	Adults (≥ 16 years old) patients presenting to Sunnybrook Health Sciences Centre (SHSC) as trauma team activations to whom a massive hemorrhage protocol is activated
SETTING	Single academic Level 1 trauma center
PLANNED SAMPLE SIZE	74 patients (37 on each study arm) The anticipated duration for this study's recruitment period is 24 months.
PATIENT INCLUSION/EXCLUSION	Inclusion criteria: ● Age ≥ 16 years ● Requires Massive Hemorrhage Protocol activation (see Table 1) in the trauma bay ● Admission to the trauma bay between 08:00-20:00hrs on weekdays Exclusion criteria: ● Transferred from another healthcare facility ● Death in the trauma bay prior to randomization ● Arrival to trauma bay with ongoing CPR ● Patients with penetrating head injury with Glasgow Coma Scale of 3 AND loss of brain matter through the wound

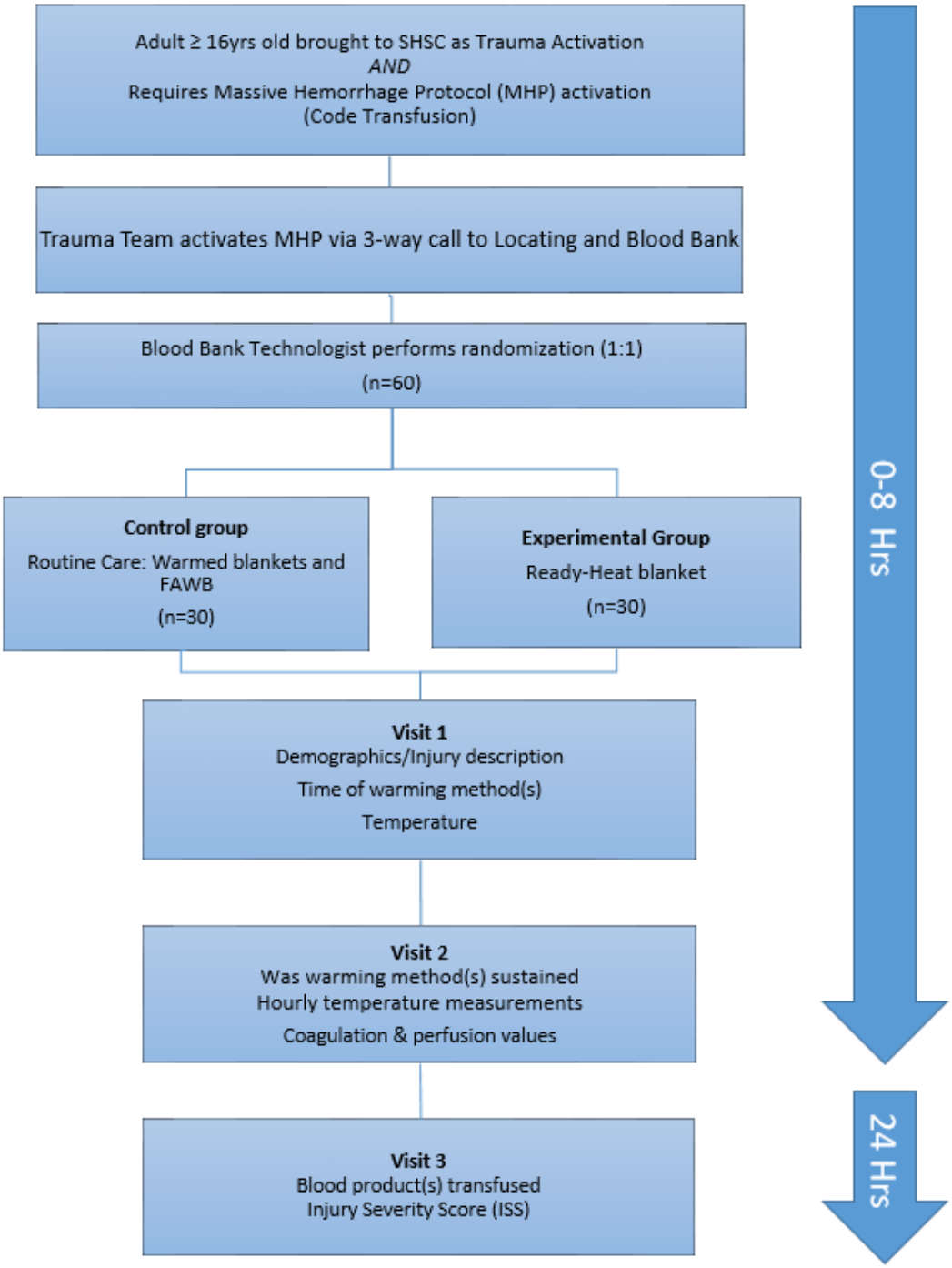
RANDOMIZATION	Web-based computerized allocation sequence generated by independent statistician
STUDY OUTCOMES	Primary outcomes (feasibility): (1) Feasibility of performing a pilot pragmatic randomized controlled trial (RCT) to evaluate effectiveness of the Ready-Heat® blanket to increase temperature by at least 1°C at eight hours from time of blanket placement in the trauma bay in severely injured trauma patients to whom a massive hemorrhage protocol is activated (2) Feasibility of adherence to the application of the Ready-Heat® blanket in patients enrolled in the intervention arm throughout the trauma bay resuscitation; (3) Feasibility of adherence to body temperature measurement throughout the different phases of care (i.e.: TB, ED, CT scanner suite, OR, IR suite, ICU) within the first eight hours of blanket application. (4) Feasibility of maintenance of at least one blanket applied throughout the different phases of care (i.e.: TB, ED, CT scanner suite, OR, IR suite, ICU) Secondary Measures: (1) Concurrent warming strategies used (i.e.: fluid warmers, FAWB, etc.) within the first eight hours of blanket application in conjunction with or replacement of Ready-Heat® chemical heating blanket; (2) Number of units of blood products (plasma, red blood cells, platelets, fibrinogen concentrate) transfused within 24 hours of trauma bay arrival; (3) Coagulation (platelet count, INR, fibrinogen) and perfusion parameters (pH, base deficit, serum lactate) measured on arrival, and at the next time points collected as per clinician discretion; (4) Hemoglobin level measured on arrival, and at the next time points collected as per clinician discretion. Secondary Safety Measures: (1) Number of times blanket is placed directly on the skin; (2) Skin redness and/or burns.
STATISTICAL ANALYSIS	The results of this pilot trial will be used to assess the feasibility and inform the design of a definitive trial. We will present point estimates of feasibility outcomes with 95% confidence intervals. Demographic and clinical characteristics will be summarized in total and by two arms using mean, standard deviation (SD), median (interquartiles) and range for continuous variables, and percentages for categorical

	variables. The Wilcoxon rank-sum test, Chi-square test or Fisher exact test will be applied for comparing continuous or categorical variables between two arms, as appropriate. The proportion (and 95% confidence intervals) of patients with an increased temperature by at least $1^{o}C$ at 8 hours from arrival to the trauma bay will be calculated and compared between two arms using Chi-square or Fisher exact test as appropriate. Linear mixed model will be used to search for significant time trends in two arms on the hourly body temperature measurements within the first eight hours of blanket application. To compare coagulation and perfusion parameters measured on arrival and over the first 8 hours, between two arms, linear mixed model will also be performed for the repeated measurements. P-value < 0.05 will be considered statistically significant.

1.0 KEY ROLES AND CONTACT INFORMATION

Regulatory Sponsor:	Sunnybrook Research Institute 2075 Bayview Avenue Toronto, ON Canada M4N 3M5
Principal Investigator:	Luis Da Luz
Academic Research Organization:	Sunnybrook Health Sciences Centre H115 2075 Bayview Avenue Toronto, ON Canada M4N 3M5

Figure 1 Pilot Trial Schema



2.0 INTRODUCTION

This study document is the protocol for a research study involving human participants. This study is to be conducted according to Canadian and international standards, and in compliance with the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements and research policies.

2.1 Background

2.1.1 Hypothermia and Mortality in Trauma

Massively bleeding hypothermic trauma patients have 2.7-fold higher odds of mortality in the first 24 hours of hospital admission, increased length of stay, and increased need for transfusion.[1-7] Hypothermia is independently associated with mortality in traumatically injured patients due to its negative physiologic effects on hemostasis, cardiorespiratory and renal function.[8] Despite this, a retrospective quality review at our institution found that approximately 30% of trauma patients will have hypothermia despite the treatment provided.[9]

2.1.2 Conventional re-warming strategies for in-hospital patients

The most common first-line active surface rewarming strategies involve the use of a combination of forced air warming blankets (FAWB), and warmed blankets. Unfortunately, these strategies are cumbersome and ineffective,[10] particularly during the initial hours of admission where multiple transfers occur.[11] FAWB requires continuous power, which limits portability. In addition, thermally warmed blankets require interchange at frequent intervals.

2.1.3 Chemical warming blankets

Prehospital, military, and intraoperative studies have suggested chemical warming blankets as a pragmatic strategy.[8, 12] A recent pilot study (manuscript under review) at our institution demonstrated feasibility of using the Ready-Heat® (TechTrade LLC, Orlando, FL, USA) chemical heating blanket in the initial phases of hospital care in bleeding trauma patients requiring a mass hemorrhage protocol (MHP). In this pilot study, the blanket was applied within a median time of 23 minutes. These chemical blankets generate an oxygen-activated exothermic effect in 8-15 minutes, providing warmth over 8 hours (up to 40 degrees Celsius). These blankets carry the advantage of portability without electricity requirement. Furthermore, in conjunction with other strategies, they provide a superior surface rewarming strategy for patients at high risk of developing hypothermia. STAYWARM-2 will be the first randomized controlled trial performed in-hospital to evaluate a self-warming blanket to address hypothermia in massively bleeding trauma patients within the initial hours post hospital arrival.

2.2 Current Proposal and Rationale

We propose a phase I, single centre, pilot, feasibility, prospective, open-label (with blinded outcome assessors) RCT. STAYWARM-2 aims to examine the impact of the Ready-Heat® warming blanket on the temperature of injured patients receiving a massive transfusion. Current warming strategies increase the logistical difficulty of transferring patients (which is frequent during the initial hours of trauma care) or must be changed at frequent intervals. Chemical blankets that provide continuous heat address these two challenges. This has potential to reduce the overall workload of direct care clinicians, freeing them for other patient care duties. Additionally, the intervention may achieve enhanced thermoregulation compared to the current strategy (as demonstrated in the prehospital literature), which can provide better care and better patient comfort (hypothermia causes patient discomfort[15]) and avoid the clinical

complications related to hypothermia. Findings from this preliminary study will provide data for a future CIHR or military grant to launch a larger randomized controlled trial in the prehospital/in-hospital trauma settings, to improve the care of patients at risk of developing hypothermia.

2.3 Study Impact and Benefit

The study will provide knowledge on feasibility and efficacy of using the chemical blankets during these initial hours of hospital care to further support better management of hypothermia. The new evidence generated may be used to inform larger studies (e.g., multicenter trials) in the same setting or in other acute care settings, such as the emergency department and in burn units. Finally, the study will contribute evidence to be applied in studies in the civilian prehospital setting (e.g., land or air Emergency Medical Services) as this setting lacks resources to adequately prevent or treat hypothermia.

3.0 OBJECTIVES AND SCIENTIFIC AIMS

3.1 Study Objectives

1 - To investigate the feasibility of using the Ready-Heat® chemical heating blanket to increase the body temperature by at least 1^{o}C in severely injured trauma patients with activation of a massive hemorrhage protocol (MHP), compared to conventional in-hospital surface rewarming methods (e.g., warmed blankets and/or FAWB) for the first eight hours of blanket application on the patient.

3.2 Primary feasibility outcome:

1 - Feasibility of enrolling the 74 patients over a span of two years.

3.3 Secondary Feasibility Outcomes

2- Feasibility of applying and keeping the 2 blankets in the trauma bay
3- Feasibility of keeping the 2 blankets in the CT scanner suite
4- Feasibility of keeping the 2 blankets in the ED
5- Feasibility of keeping at least one of the blanket in the OR or IR suite (one can be removed for procedures and re-applied at the end of the intervention
6- Feasibility of keeping the 2 blankets in PACU (for example one blanket is removed in the OR and reapplied at the end of the procedures and kept in PACU before the patient is transferred to the ICU)
7- Feasibility of keeping the 2 blankets in the ICU up to 8 hours of until patient achieves 37.5 degrees Celsius.
8- Reasons why the blanket was not maintained at each of the next phase of care (CT scanner suite, IR suite, OR, ED, ICU)

3.4 Efficacy Outcomes

9- Increase of temperature from admission up to 8 hours of 1 degree Celsius

3.5 Clinical Outcomes

10- Proportion of adherence to body temperature measurement throughout different phases of care (i.e.: ED, CT scanner suite, OR, IR suite, ICU)
11 -Use of concurrent warming strategies(i.e. fluid warmers, FAWB, etc.) within the first eight hours of blanket application in conjunction with, or replacement of, the Ready-Heat® chemical heating blanket

12- Number of units of blood products (red blood cells, plasma, platelets, and fibrinogen concentrate) transfused within 24 hours post arrival to the trauma bay
13- Coagulation (platelet count, INR, fibrinogen level) and perfusion parameters (pH, base deficit, serum lactate) measured on arrival, and at the next time points collected as per clinician discretion
14- Hemoglobin level measured on arrival, and at the next time points collected as per clinician discretion

3.6 Safety Outcomes:

15 - Number of times blanket is placed directly on the patient skin
16 - Number of times patients developed redness and/or skin burns

4.0 HYPOTHESES

We hypothesize that the use of Ready-Heat® blanket will be feasible in this pilot RCT (according to the primary outcome measure) in severely injured trauma patients to whom a MHP is activated while in the trauma bay.

5.0 STUDY METHODS

5.1 Study Design

This will be a pilot, feasibility, prospective, open-label (with blinded outcome assessors) RCT to evaluate the feasibility of using two Ready-Heat® half blankets to increase temperature by at least 1^{o}C at eight hours from arrival to the trauma bay, in severely injured bleeding trauma patients where a MHP is activated. A total of 74 participants will be randomized in a 1:1 ratio, to receive the intervention - two Ready-Heat® 4-panel half blankets applied indirectly (as per manufacturer's directions) with two flannel blankets placed under them, or the control - two warmed blankets (current standard of care) only. The study will take place at Sunnybrook Health Sciences Centre (SHSC). The patient will be screened in the trauma bay and enrolled by the TTL. Upon confirming eligibility for the study, a study research coordinator/assistant will randomize using a web-based randomization sequence built into REDCap. If the patient is randomized to receive the intervention, two Ready-Heat® blankets will be activated by opening the seal on the packaging and affixed to the blood product cooler to be given to the trauma team in the trauma bay. As this is an open-label trial, only the statistician will remain blinded during the final analysis. Enrollment will occur during weekdays between 0800-2000hrs with the aim of assessing feasibility of using the blanket when study coordinators are not always available to reinforce temperature monitoring, proper blanket placement, and compliance with keeping the blanket on the patient over the intervention period. Subjects in the control arm will have two warmed blankets obtained from a blanket warmer appliance in the trauma bay and will be applied on the patient by the trauma team. Temporary removal of the blanket and partial exposure of the patient may be necessary to facilitate clinical procedures. In the intervention arm, two separate four-panel blankets will be used to allow for temporary exposure for clinical procedures while still maintaining coverage for the rest of the body (i.e., 1 four-panel blanket can be applied to the torso while a fractured femur is reduced). Clinicians will be educated to keep the intervention warmer on the patient until 8 hours from time of blanket application. If there is a need to remove the intervention prior to the completion of 8 hours, the clinical team will document the reason (e.g., adverse reaction, interference with procedure, etc.). In this case, clinical teams will be educated to transition to the current standard of care (warmed blankets or

FAWB). If at least one of the two blankets remained until 8 hours post blanket application, clinical teams will be instructed to remove them and apply the current standard of care.

5.2 Study Population

Patients included in this study are severely injured adult trauma patients, admitted to the trauma bay at SHSC as trauma team activations (TTA), where a MHP is activated by the TTL or delegate, within the period the patient is assessed and managed in the trauma bay.

5.2.1 Inclusion Criteria

1. Age ≥ 16 years
2. MHP activated in the trauma bay (see Table 1)
3. Between 08:00-20:00hrs on weekdays

Table 1 MHP Activation Criteria

MHP activation criteria
● Life-threatening bleeding situation requiring mobilization of blood bank, laboratory and clinical resources. ● Anticipated need for at least 4 units of red blood cells immediately and component therapy (platelets, plasma, and fibrinogen).

5.2.2 Exclusion Criteria

1. Transferred from another healthcare facility
2. Death in the trauma bay prior to randomization
3. Arrival to trauma bay with ongoing CPR
4. Patients with penetrating head injury with Glasgow Coma Scale of 3 AND loss of brain matter through the wound

5.3 Study Activities

5.3.1 Patient screening, recruitment, and enrolment

Recruitment will occur in the trauma bay during weekdays between 08:00-20:00hrs by Staff Trauma Team Leaders, with experience in QI initiatives and enrollment of severely bleeding trauma patients in clinical trials. Due to the high acuity of the patient condition, who usually needs multiple emergent interventions, consent will be obtained retrospectively (delayed consenting process). In addition, by seeking the patient's consent for enrollment during a tenuous point in their care, there is a potential of introducing bias, or concerns about coercion into accepting any care related to the initial resuscitation.

As soon as possible, following the randomization and inclusion, the patient (if able to comprehend) or substitute decision maker (SDM), will be approached about the study. They will have their specific warming intervention explained, and will have, at that point, the right to request that their data are withdrawn from the study.

Study personnel will contact the MRP for permission to approach the patient or ask that they introduce the study to the patient. With permission to enter the patient's circle of care, the research coordinator will then approach patients who were randomized and included in the study. The research coordinator will introduce the trial, confirm eligibility and conduct the informed consent discussion. This discussion will include the rationale for the study, the anticipated risks and benefits of participation, and their rights as a study participant (including withdrawal at any time). Capable participants will be offered an opportunity to ask questions and consult with their family and/or their physician before making a decision to continue in the study. If the patient is deemed incapable of providing informed consent for the study, study personnel will approach the SDM and go over the same process to obtain the consent. Patients or SDM will be given an Informed Consent Form to be signed, at this point.

One signed copy of the informed consent will be placed in the participant's medical record, another copy given to the participant and the original kept in the study file with the research coordinator. If the participant does not wish to participate, the reason for declining will be documented.

Patients will be randomized upon activation of the MHP according to a computer-generated allocation sequence using RedCap. If the patient is randomized to receive the intervention, the study research coordinator/assistant will activate the two Ready-Heat® blankets by opening the seal on the packaging. A trauma team member will place the blankets on the patient. As this is an open-label trial, only the statistician will remain blinded during the final analysis. Enrollment will occur 08:00-20:00hrs on weekdays with the aim of assessing feasibility of using the blanket when study coordinators are not always available to reinforce temperature monitoring, proper blanket placement, and compliance with keeping the blanket on the patient over the intervention period.

Data will be collected by the research assistants and medical students as the patients are enrolled in the trial during weekdays 8 am to 8 pm. REDCap will be used to register the collected variables.

Research Ethics Board (REB) approval of the protocol and the informed consent form will be obtained. A recruitment log of eligible and ineligible patients as well as reasons for non-consent will be kept. We anticipate that this study will take 24 months to complete.

5.3.2 Randomization and stratification

The patient will be screened in the trauma bay and randomized by the study research coordinator/assistant. Patients will be allocated to a treatment group using a secure, concealed, computer-generated, web-based (created on REDCap) randomization sequence. Only a non-study biostatistician will have access to the randomization sequence within the treatment allocation schedule (the study biostatistician will be blinded to treatment allocation for any interim analyses performed). A 1:1 randomization ratio will be used.

5.3.3 Interventions

A schematic representation of the protocol summary is shown in Figure 1.

5.3.3.1 Investigational Products

Ready-Heat® is manufactured by TechTrade LLC[13]. The manufacturer has confirmed the authorized use of this product in Canada, which was a requirement for STAYWARM-1. Further, this product is now currently distributed by Canadian vendors for the Canadian marketplace.

In the attached document from the manufacturer, this device is considered a "Class I medical device". As such, there is no requirement to obtain an investigational testing authorization (ITA)

Requirements for an Investigational Testing Authorization (ITA)	
Class I	There is no requirement to obtain an ITA for a Class I medical device. Subsection 80(3) of the Regulations permits a manufacturer or importer of a Class I medical device to sell the device to a qualified investigator for the purpose of conducting investigational testing. The manufacturer or importer is still required to possess all the records and information detailed in section 81. Institutional requirements and Research Ethics Board (REB) approval apply.

Adobe Acrobat Document

The Ready-Heat® product comes in a variety of configurations. The 4-panel blanket is a single-use disposable blanket that uses proprietary air-activated warming panels that provide slow continuous and consistent warming. Weighing 794 grams, and dimensions of 86cm/122cm, each blanket is stored in an oxygen-free poly-bag. Upon opening the package, it gradually heats up to 40°C over a period of 15-20 minutes, and after reaching peak temperature will remain warm for 10 hours.

5.3.3.2 Packaging

Two individually wrapped 4-panel Ready-Heat® blankets will be issued to patients enrolled in the intervention arm. The two individual packages, containing one blanket each, will be opened by the study research coordinator/assistant upon patient randomization to initiate the air-activated exothermic process.

5.3.3.3 Treatment Assignment Procedures

Once enrolled, patients will be randomized to either the control or intervention arm through the randomization procedure described in section 5.3.2.

5.3.3.4 Control arm

Patients randomized to the control arm will receive conventional rewarming strategies such as FAWB and 2 warmed blankets.

5.3.3.5 Intervention arm

If the patient is randomized to receive the intervention, the two Ready-Heat® blankets will be activated by opening the seal on the packaging and given to the trauma team in the trauma bay. As this is an open-label trial, only the statistician will remain blinded during the final analysis. Subjects in the control arm will have a warmed blanket obtained from a blanket warmer appliance in the trauma bay. Temporary removal of the blanket and partial exposure of the patient may be necessary to facilitate clinical procedures. In the intervention arm, two separate Ready-Heat four-panel blankets will be used to allow for temporary exposure for clinical procedures while still maintaining coverage for the rest of the body. Clinicians will be educated to keep the interventional products until the 8 hours post blanket application are completed. If an interventional product becomes soiled before the prescribed 8 hour period, a replacement product may be dispensed by contacting the Blood Bank. If there is a need to remove the intervention prior to the completion of 8 hours, the clinical team will document the reason (e.g., adverse reaction, interference with procedure, etc.). In this case, clinical teams will be educated to transition to the current standard of care (warmed blankets, or FAWB). If at least one of the two blankets remained until 8 hours post, clinical teams will be instructed to remove them and apply the current standard of care.

5.3.5.2 Storage and Stability

As per manufacturer's Instructions for Use (IFU) document, the Ready-Heat® blanket may be stored in its air-tight protective packaging until ready for use. Upon removing the outer packing, the product will reach operating temperature within 15-20 minutes and will remain functional for up to 10 hours. After use, the blanket can be disposed of with regular waste as there are no harmful ingredients. The Blood Bank will maintain a stock of the Ready-Heat® blankets and stored at room temperature. The study product will be dispensed to those randomized to the intervention arm along with the first MHP pack of blood products.

5.3.5.3 Dispensing of Investigational Product

The Ready-Heat® blanket will be provided to randomized patients by Study research coordinator/assistant.An instruction sheet will be provided specifying how to apply the Ready-Heat blanket while avoiding direct skin contact. Instructions will be provided to keep the interventional products until the 8 hours post blanket application is completed.

5.3.5.4 Return and Destruction of Investigational Product

Trauma Team members will be made aware of their responsibility to return any unused investigational products in the event the resuscitation is ended before applying the product (i.e.: patient death, termination of resuscitation). As per manufacturer's Instructions for Use (IFU) document, the Ready-Heat® blanket may be disposed of with regular waste as there are no harmful ingredients.

5.4 Study Visits and Assessments

Study visits will be conducted by research assistants during weekdays to collect data

5.4.1 Study Visits

The following information will be collected during study visits either in person or remotely reviewing electronic health records. During weekdays, 8 am to 8 pm, the research assistant will be following the patient across the different phases/locations of care and will be collecting data at the same time. Research assistants will access all documented data on the next weekday. Visits and specific data collection are detailed as follows:

5.4.1.1 Visit 1

On admission to the trauma bay: Demographics, injury characteristics and surgical management:

1. Date of injury
2. Time of injury
3. Sex
4. Age
5. Types of surgical procedures performed in the first 8 hours following hospital arrival
6. Date of arrival
7. Time of arrival
8. Time of randomization
9. Name of attending TTL and sub-TTL (if applicable)
10. Initial temperature recorded
11. Was the blanket placed on the patient? Yes/No
12. Time that the blanket was placed on the patient, if registered
13. Reason why blanket was not applied
14. Blanket applied directly to the patient`s skin? Yes/No
15. Use of fluid warmers
16. Use of FAWB

5.4.1.2 Visit 2

Within the first eight hours of blanket application:

1. Location of the patient
2. Is the blanket kept on the patient? (Yes/No)
3. If not, what was the reason it was removed?
4. Temperature recorded, hourly (Yes/No)
5. If yes, the temperature recorded
6. Type of temperature measurment
7. Blanket applied directly to patient`s skin? Yes/No
8. Use of FAWB
9. Use of fluid warmers

At discretion of the clinician, within the first eight hours of blanket application:

10. Coagulation (platelet count, INR, fibrinogen)
11. Perfusion parameters (pH, base deficit, serum lactate)
12. Hemoglobin

13. Number of units of red blood cells, plasma, platelets, and fibrinogen concentrate administered within the first 8 hours

5.4.1.3 Visit 3

At 24 hours post blanket application:

1. Number of units of red blood cells, plasma, platelets, and fibrinogen concentrate administered within the first 24 hours
2. Type of injury (blunt/penetrating)
3. Injury Severity Score (ISS)
4. Frequency of safety events with skin

5.6 Protocol Deviations

Planned or unplanned deviations may occur on the part of the participant, the investigator, or study research team. In resolution to a deviation, corrective/preventative actions are to be developed and implemented in a timely manner to avoid subsequent deviations. Protocol deviations will be documented and reported as required and assessed where necessary during analysis. If a control or study intervention is noted to not be in use, or key data are missing from the health record, a reason for noncompliance will be documented. Based on findings from STAYWARM1, reasons for noncompliance are hypothesized to arise from patient condition, and lack of familiarity with the study protocol. Several educational initiatives will be developed prior to study commencement for trauma team members, to avoid protocol deviations during the study period.

6.0 CRITERIA FOR OUTCOME ASSESSMENT

6.1 Primary outcome assessment

1. *Feasibility of Ready-Heat® blanket to increase temperature by at least 1^{o}C at eight hours from arrival to the trauma bay in massively bleeding trauma patients.*
   If the study intervention is unable to increase body temperature by at least 1^{o}C in 80% of patients at eight hours from arrival, the study as it is currently designed will not be deemed feasible.

2. *Feasibility of adherence to the application of the Ready-Heat® blanket in patients enrolled in the intervention arm throughout the initial trauma bay resuscitation* Failure to apply and maintain the Ready-Heat® blanket in more than 20% of patients enrolled in the intervention arm throughout the initial trauma bay resuscitation, the study will not be deemed feasible.

3. *Feasibility of adherence to body temperature measurement throughout different phases of care within first eight hours of blanket application.*
   Failure to measure body temperature throughout different phases of care (i.e.: ED, CT, OR, IR, ICU) within the first eight hours of blanket application in more than 20% of enrolled patients, the study will not be deemed feasible.

7.0 STATISTICAL ANALYSIS PLAN

7.1 Sample Size and Sample Size Justification

For the STAYWARM-2 trial, the sample size calculation was based on a compliance rate of 80% to within a 95% confidence interval of +/– 10%. The sample size obtained was **58 patients (29 per arm) in total** to estimate a compliance rate of 80% to within a 95% confidence interval of +/– 10%. With an anticipated 20% dropout rate (i.e., withdrawal of consent, exclusion of eligibility, etc), the sample size will be inflated to a **total of 74 patients, 37 in each arm**. If we assumed a 90% confidence interval of +/– 10%, then we require a sample size of 48 patients (24 per arm) after considering 20% dropout rate. See the following outputs for details:

Confidence Interval of A Proportion

Numeric Results

Precision	C.C. Confidence Coefficient	N Sample Size	P0 Baseline Proportion
0.08000	0.95323	90	0.80000
0.09000	0.95130	69	0.80000
0.10000	*0.95529*	*57*	*0.80000*
0.08000	0.90168	58	0.80000
0.09000	0.90969	45	0.80000
0.10000	*0.90329*	*37*	*0.80000*

Report Definitions
Precision is the plus and minus value used to create the confidence interval.
Confidence Coefficient is probability value associated with the confidence interval.
N is the size of the sample drawn from the population.
P0 is the estimated baseline proportion.

Summary Statements
A sample size of 57 produces a 96% confidence interval equal to the sample proportion plus or minus 0.10000 when the estimated proportion is 0.80000.

A sample size of 37 produces a 90% confidence interval equal to the sample proportion plus or minus 0.10000 when the estimated proportion is 0.80000.

Given that this pilot feasibility trial, a sample size of 58 total patients was deemed appropriate. After considering 20% drop out rate, we will aim to enroll 74 patients to determine the feasibility of the trial and to provide more accurate estimates of the numbers required for a definitive trial. The trial will proceed until there are 74 enrolled patients and at least 58 patients who complete the trial to 13 weeks.

7.2 Final Analysis Plan

Demographic and clinical characteristics will be summarized in total and by two arms using mean, SD, median (interquartiles) and range for continuous variables, and percentages for categorical variables. Wilcoxon rank-sum test, Chi-square test or Fisher exact test will be applied for comparing continuous or categorical variables between two arms, as appropriate. To investigate the primary objective on the feasibility of using the Ready-Heat® chemical heating blanket, the proportion (and 95% CIs) of patients with an increased body temperature by at least 1^{o}C at 8 hours from arrival to the trauma bay will be calculated and compared between two arms using Chi-square or Fisher exact test as appropriate. Line graph (with mean and SD) of body temperature over the first 8 hours of blanket application will be plotted for two treatment arms. To search for significant time trends in two arms on the hourly body

temperature measurements within first 8 hours of blanket application, linear mixed effects repeated model will be performed with both fixed (time in hours, treatment arms, and arms by time interaction) and random (patient) effects. To compare treatment effects on the coagulation parameters (platelet count, INR, fibrinogen level), perfusion parameters (pH, base deficit, serum lactate), and hemoglobin levels measured on arrival and over the first 8 hours, linear mixed effects repeated model will also be performed with both fixed and random effects. Skewness and Kurtosis will be tested on the distribution of coagulation, perfusion and hemoglobin parameters. Natural logarithm transformation will be applied to normalize the distribution if necessary. Descriptive analysis will be summarized in total and by arms for safety measurements (i.e., number of units of blood products transfused, number of times blanket is placed directly on patient skin, and number of times patients developed redness and/or skin burns). All analyses will be conducted using Statistical Analysis Software (SAS version 9.4, Cary, NC) and R package (version 4.3.0). P-value < 0.05 will be considered statistically significant.

8.0 ASSESSMENT OF SAFETY

8.1 Definitions

8.1.1 Adverse Event

An **Adverse Event (AE)** is defined as any new event that may jeopardize the patient which the study investigator physician perceives may be directly related to the enrolment in the pilot study or to the assigned arm. Adverse events are not study related if they are related primarily to the underlying disease. All AEs are to be documented and assessed for relatedness. If related to the study intervention and occurring from baseline up to 24 hours (by the final visit), the AE will be recorded on the eCRF and coded as per the most recent edition of the Common Terminology Criteria for Adverse Events (CTCAE).

8.1.2 Expected adverse events with Ready-Heat® blankets

Prolonged direct skin contact with the Ready-Heat blanket has been known to cause mild burns. The manufacturer specifies the need for careful supervision when used with “the elderly….people with sensitive skin and those who can’t feel heat or regulate heat”[13]. Given that some of the enrolled patients may be sedated due to clinical condition, the study products will be applied with the express direction to avoid direct skin contact. The recommendation will be made to use a standard blanket as an intermediary between the skin and the study product.

8.1.3 Unexpected Adverse Event

An unexpected adverse event is defined as any adverse event that is not identified in section 8.1.2 or in nature, severity or frequency in the current Health Canada Product Monograph.

8.1.5 Serious Adverse Event (SAE)

A serious adverse event (SAE) in the study is defined as:

a) any event that is fatal or immediately life threatening, permanently disabling, severely incapacitating, or requires prolonged inpatient hospitalization, or
b) any event that may jeopardize the patient and requires medical or surgical intervention to prevent one of the outcomes listed above, AND
c) which the attending physician perceives may be directly related to enrolment in the study, or to the assigned arm.

SAEs will be considered to be study-related if the event follows a reasonable temporal sequence from the study intervention and could readily have been produced by the intervention. Adverse events are not study related if they are related primarily to the underlying disease.

8.2 Assessment of an Adverse Event

8.2.1 Relationship (Causality/Relatedness)

The causality assessment is the determination, according to the investigator's clinical judgment, of the existence of a reasonable possibility that the investigational product (IP) caused or contributed to an adverse event.

If the investigator or delegated sub-investigator is unsure about whether or not the study product caused or is related to the event, then the event will be handled as "related" to the study product for reporting purposes of the trial. If the causality assessment is "unknown but not related" to the study product, this should be clearly documented in the source documents.

8.2.2 Expectedness

Events are classified as unforeseen or unexpected if the nature, severity, or frequency is not consistent with the risk information set out in Section 9.1.2 or the Product Monograph (PM) or label.

8.2.3 Seriousness

Events are classified as serious if associated with effects threatening the life or physiological functions of a participant. Refer to the definition for "Serious Adverse Events" in section 9.1.5.

8.2.4 Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. The terms "serious" and "severe" are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

To assess the severity of an adverse event the investigators will use the following:

- the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

8.2.5 Adverse Event Recording

Investigations into potential adverse events should be done during each contact with a participant. Investigations may be done through specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded promptly in the source document, and assessed by an investigator in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and serious unexpected adverse drug reactions (SUADRs) if needed. Adverse event CRFs should be completed using source documents by a delegated research team member in a timely manner/within 15 days of site awareness. All clearly related signs, symptoms, and abnormal diagnostic procedures should be recorded in the source document, though should be grouped under one diagnosis. Each diagnosed

adverse event should then be categorized in accordance with the revised NCI Common Terminology Criteria for Adverse Events (CTCAE).

The following are not considered AEs and therefore do not require recording:

- Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency
- At the discretion of the investigator, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of study drug exposure
- Elective medical or surgical procedures.

8.3 Procedures for Reporting a Serious Adverse Event and Unanticipated Events

8.3.1 Investigator reporting: Notifying the REB

Serious adverse events and unanticipated events should be recorded and reported to the REB in accordance with local reporting requirements and timelines.

8.3.2 Investigator reporting: Notifying the Sponsor

The investigator is responsible for reporting SAEs and SUADRs to the sponsor (Sunnybrook Research Institute) in accordance with applicable regulations and reporting requirements and timelines.

Events that are assessed to be **serious and unexpected and related or cannot be ruled out as related** to the investigational product are considered SUADRs. Reporting for SUADRs should include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. The minimum information required includes at least one identifiable participant, one identifiable reporter, one serious reaction, and one suspect product.

Additionally, for SAEs and SUADRS, a Suspect Adverse Reaction Report – CIOMS I Form (Appendix B) must be completed by the investigator and forwarded to the Sponsor within 24 hours of site awareness. Information on other possible causes of the event, such as concomitant medications and illnesses should also be provided as soon as is made available.

8.3.3 Sponsor Reporting of SUADRs: Notifying Health Canada

The regulatory sponsor is responsible for reporting SUADRs to regulatory authorities in accordance with local expedited reporting requirements and timelines. In addition, the Sponsor will complete the ADR Expedited Reporting Summary Form and submit this form in conjunction with the completed CIOMS Form to the appropriate Health Canada directorate.

8.3.4 Sponsor Reporting of SUADRs: Notifying Sites

The regulatory sponsor is responsible for distributing expedited reports of SUADRs to each investigator for submission to local Ethics Committees within 15 days of sponsor awareness.

8.3.5 Reporting and Entry Timelines

Study investigators will report SAEs to the sponsor within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded and reported to the sponsor within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported to the sponsor within 72 hours of site awareness.

Adverse event information will be entered into the CRF in a timely manner and **no later than 15 days** from the time the investigator becomes aware of the event.

Serious adverse event information will be entered into the CRF in a timely manner/**within 72 hours** from the time the investigator becomes aware of the event.

9.0 Early Termination and Reasons for Withdrawal

While it is not anticipated to cause discomfort, patients may find that they are not able to continue with the study product due to the ongoing heat. Patients are permitted to withdraw consent at any time if they desire and will not undergo further trial investigations if they do so. Participants withdrawing from the study should be contacted by the study research team requesting a final visit and to follow up with any unresolved adverse events. Once withdrawn from the study, no further study procedures or evaluations should be performed, or additional study data collected. However, every effort should be made to obtain permission to document the reason for withdrawal and to collect participant outcomes, such as survival data up to the protocol-described end of participant follow up period, where possible. Any data collected prior to the withdrawal of consent may be retained and used by the sponsor. If the patient withdraws from the study, the research team will notify the patient's most responsible physician.

9.1 Data Collection and Follow-up for Withdrawn Participants

Patients will be asked to continue with follow-up of body temperature and laboratory tests. It is important to continue to follow these patients and capture outcomes that occur once they have discontinued study intervention to determine feasibility. Through telephone calls and emails, every effort will be made to obtain permission to document the reason participants withdrew consent and to continue collecting the body temperature and laboratory values previously mentioned. Patients who have had at least one of the blankets applied will be included in the per-protocol analysis.

10.0 ETHICAL ISSUES

10.1 Ethical conduct and ethical issues

Approval for patient accrual must be obtained from research ethics board (REB) at SHSC before patient recruitment can begin. Any additional correspondence with REB must be maintained by the research coordinator/assistant.

10.2 Informed Consent

Due to the clinical condition of the patients during initial presentation, screening and enrollment will be at the discretion of the Trauma Team Leader on an urgent basis. When the patient is able to safely converse, study personnel will approach the Most Responsible Physician (MRP) for permission to approach the patient. With permission, the research coordinator will then approach enrolled patients, g to introduce the trial and conduct the informed consent discussion. By being invited into the patient's circle of care with the permission of the MRP, study personnel will Introduce the rationale for the study, the anticipated risks and benefits of participation, and their rights as a study participant (including withdrawal at any time). Capable participants will be offered an opportunity to ask questions and

consult with their family and/or their physician before final decision. If the patient is deemed medically incapable, consent will be obtained from the substitute decision maker (SDM) . One signed copy of the informed consent will be placed in the participant's medical record, another copy given to the participant and the original kept in the study file with the research coordinator. If the participant does not wish to continue to participate, the reason for declining will be documented and the patient will be considered a screening failure (failure to provide informed consent).

11.0 STUDY ADMINISTRATION

This will be a single-site study, conducted at Sunnybrook Health Sciences Centre. The Research Coordinators, supervised by the Principal Investigator, will be responsible for trial coordination, site training, site start-up/activation, document management, supply management, database development, data management and statistical analysis. Study data and patient surveys will be entered and maintained on a secure password protected database developed using REDCap (www.projectredcap.org) and will be accessible via the Internet for data entry purposes.

11.1 Arrangements for day-to-day management of the trial

The research coordinator will be responsible for this aspect of the study, including system checks, maintenance, and data back-up. Patient data will be collected as enrollment occurs and entered into the electronic case report forms. Data queries will be generated monthly. A bi-weekly status report will include an update on the recruitment and status of all randomized patients. Monthly to bi-monthly audit and feedback meetings will be held. Protocol violations will be audited and recorded on designated Protocol Violation Forms.
Clinical research coordinators will work with investigators on start-up activities (REB applications; study contract; organizing study materials; local in-services). Thereafter, research coordinators will screen, consent and enrol patients, complete case report forms, and respond to data queries.

11.2 Quality Assurance

Study data will be maintained on a secure password protected database accessible from the world-wide-web. Quality control will be ensured by oversight by the research coordinator at Sunnybrook Research Institute, who will review the electronic data for all participants on a regular basis for completeness and consistency.

Quality and completeness of data entry will be reviewed as soon as possible after data entry, within five business days of data entry for the first five participants randomized, and within 15 days of data entry thereafter. Data queries generated by identification of incomplete or inconsistent data will be raised and should be resolved by the study coordinator or PI in a timely manner. Corrections or changes in the data management system are tracked with the retention of the original data and the corrected data with the date of data entry and submitting personnel.

13.0 DATA HANDLING AND RECORD KEEPING

13.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Personal Health Information Protection Act of 2004 (PHIPA) and the Research Ethics Board. PHIPA outlines the rules for the collection, use and disclosure of personal health information. The Act requires each participant to consent to the collection, use and access of personal health information (PHI), unless consent is waived by the REB. As consent is required, each participant will be informed of the following:

- What PHI will be collected during this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator may use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

13.2 Source Documents

Source data/documents are original documents, data and records in a clinical study that are necessary for the reconstruction and evaluation of the study. Original documents and data records in this study include, but are not limited to:

- worksheets
- hospital records
- medical records
- memorandum
- participants' diaries or evaluation checklists
- pharmacy dispensing records
- copies or transcriptions certified after verification as being accurate and complete
- participant files and records kept at the pharmacy
- entries entered directly into the source documents

Research coordinators will maintain appropriate medical and research records for this study, in addition to regulatory and institutional requirements for the protection of confidentiality of participants. If electronic source data documents are printed it should be signed and dated by the investigator to confirm content and filed with other source documents.
The investigator(s) and research team members listed on the Task Delegation Log (TDL) will have access to participant medical records and will collect only the information needed for the study. Sponsor delegated monitors, representatives of institutional committees and regulatory authority representatives of the country in which the study is being conducted will also have access to examine records for the purposes of quality assurance reviews, audits and evaluation of study safety and progress.

13.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study personnel under the supervision of the investigator. All source documents and applicable laboratory reports will be reviewed as needed and used to ensure that data collected for the purposes of the study are accurate and complete. Contemporaneous review of laboratory results and the assessment of clinical significance for those results considered out of range will be documented by means of dated signature by the reviewing investigator. Study personnel, including data entry team members, should use source documents to complete case report forms (CRFs).

As part of the safety plan for this study, the investigator will review individual study participant records to ensure that appropriate mechanisms to protect the safety of study participants are being followed, that protocol requirements are being adhered to, and that data is accurate, complete, and secure. Participant records include, but are not limited to: consent forms, case report forms, data forms, laboratory specimen records, inclusion/exclusion forms, and medical charts. All study data will be collected by a member of the study research team and recorded in accordance with applicable procedures.

13.4 Data Capture

13.4.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for this study. Electronic/Paper case report forms (eCRFs/pCRFs) will be used to collect data. CRFs will be completed by data capture personnel and signed off by the investigator in a timely manner. Good documentation practices will be implemented according to standard operating procedures. All data requested on the CRF must be recorded and verifiable by source document.

13.5 Records Retention

It is the responsibility of the REB, investigator, and regulatory sponsor to retain study essential documents as per local regulatory requirements and GCP Guidelines.

Study essential documents must be maintained in a secure and confidential manner for participating Canadian sites for a period of 15 years. For the purposes of this study, the start date of the retention period is the date of the final report of the trial. Exceptions may be made for sites which close prematurely, wherein the start date for the retention period will be the date of notification to Health Canada of the sites closure. All study records are then to be destroyed according to local and national policy and requirements. It is the investigator's responsibility to request authorization for destruction at the completion of the retention period and/or for the sponsor to inform the investigator/institution when these documents may be destroyed.

13.6 Clinical Trial Registration

In accordance with Health Canada's Notice "Registration and Disclosure of Clinical Trial Information, November 30, 2007", the investigator will register this study on Clinicaltrials.gov (www.clinicaltrials.gov), a publically available registry that conforms to international standards for registries.

14.0 References

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