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Combat Fluid Resuscitation Interoperable Capability

Final Report

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Defence R&D Canada
Technical Report
DRDC Toronto TR 2010-172
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Canada

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In conducting the research described in this report, the investigators adhered to the policies and procedures set out in the Tri-Council Policy Statement: Ethical Conduct for research involving humans, National Council on Ethics in Human Research, Ottawa, 2010, as issued jointly by the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada

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Abstract

This project evaluated novel small-volume hypertonic fluids for combat resuscitation for improvement in patient survivability and reduction of the post-traumatic inflammatory response, and for reducing overall fluid volume requirements. The outcome has demonstrated that there is no clinically significant difference in resuscitating shock and traumatic brain injury (TBI) patients with either normal or hypertonic saline. However, from a military operational medical care perspective, the less than 10% hypertonic fluid volume (versus normal saline volume) required to generate the same clinical outcome confers a substantial logistical advantage in the field. Deputy Surgeon General has confirmed that Canadian Forces Health Services (CFHS) will seek Health Canada approval of hypertonic saline fluids for military use, in consultation with Defence Research and Development Canada (DRDC) and Department of Defense (DoD).

Résumé

Le présent projet visait à évaluer l'efficacité, sur le plan de l'amélioration de la survie des patients, de la diminution de la réponse inflammatoire post-traumatique et de la réduction du volume de solution nécessaire, de nouvelles solutions hypertoniques de réanimation à administrer en petites quantités en situation de combat. Les résultats indiquent qu'il n'existe aucune différence clinique notable entre l'administration d'une solution saline normale ou hypertonique en ce qui concerne la réanimation des patients en état de choc et des victimes de traumatismes cérébraux. Cependant, du point de vue des soins médicaux militaires opérationnels, le fait de diminuer de 10 % le volume de liquide hypertonique requis (par rapport à la solution saline normale) tout en obtenant les mêmes résultats cliniques confère un avantage logistique important sur le terrain. Le médecin-chef adjoint a confirmé que les Services de santé des Forces canadiennes (SSFC) s'adresseront à Santé Canada pour faire homologuer des solutions salines hypertoniques pour utilisation militaire, en consultation avec RDDC et le MDN.

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Executive summary

Combat Fluid Resuscitation Interoperable Capability

**Shawn G. Rhind; Maria Y.Y. Shiu; Pang N. Shek; DRDC Toronto TR 2010-172;
Defence R&D Canada – Toronto; October 2010.**

Background: Severe bleeding and traumatic brain injury (TBI) are leading causes of preventable death in both civilian and military trauma settings. Effective hemorrhage control and blood volume replacement with intravenous fluids remain essential for early trauma care. Current military resuscitation practices, involving infusion of dilute saline solutions to replace acute blood losses before transfusions, were adopted from civilian trauma care and have not been revised in over 30 years. Conventional resuscitation fluids can worsen cellular injury and clinical outcome.

Methods: Hypertonic saline has been shown, in animal studies and limited clinical trials, to be effective in compensating for blood loss through volume expansion; reducing excessive inflammation; and alleviating brain edema. A unique challenge for the military is the weight and volume of resuscitation fluids (3 l of normal saline, weighing 3 kg, to replace 1 l of blood loss) a medic can carry onto the battlefield. The successful demonstration of an optimal resuscitation fluid, clinically effective but with a logistic advantage in an austere combat environment remains elusive. Hence, there is a need for alternative resuscitation fluids for front-line casualty care.

The primary objective of the Combat Fluid Resuscitation Interoperable Capability Technology Demonstration Project (CFRIC TDP) is to validate the clinical efficacy of small-volume hypertonic fluids for initial resuscitation of patients suffering from severe traumatic injury in a major, collaborative multi-centre clinical trial. A secondary objective is to investigate the underlying pathobiology of trauma-induced cellular complications in response to different resuscitation fluids.

Results: The trial enrolled more than 2,000 patients over a 3-year period (May 2006 – May 2009). Concurrently, Defence Research and Development Canada (DRDC) analyzed over 500 biological samples from 120 patients (generating > 1 million data points) for the determination of biomarkers. An independent Data Safety and Monitoring Board terminated the trial ahead of schedule based on the determination that further patient enrolment would not statistically change the outcome of study. Clinical findings of the trial showed that there was no superiority of hypertonic fluids over normal saline intervention in both Shock Cohort (28-day survival) and TBI Cohorts (6-month neurological outcome). In other words, hypertonic saline is no better or worse than normal saline as a resuscitation fluid as determined by the observable clinical outcome.

Significance: Overall, the CFRIC TDP achieved its planned objectives. Specifically, this project demonstrated: (1) the potential logistic advantage of hypertonic saline, requiring less than 10% of normal saline in volume for the same clinical outcome, in resuscitating combat casualty with hemorrhagic shock and TBI; (2) a laboratory evidence-based substantiation of hypertonic saline's efficacy in reversing the exaggerated harmful inflammatory response, a benefit to surviving casualties; (3) DRDC's capability in conducting human translational clinical trials of relevance to Surgeon General's operational requirements, in partnership with major external funding agencies; (4) DRDC leadership in conducting and promoting leading-edge biomedical research in trauma and casualty care.

Sommaire

Capacité interopérable de liquides de réanimation en situation de combat

Shawn G. Rhind; Maria Y.Y. Shiu; Pang N. Shek; RDDC Toronto, rapport technique 2010-172; R et D pour la défense Canada – Toronto; octobre 2010.

Contexte: Les hémorragies et les traumatismes cérébraux graves sont les principales causes de décès évitables chez les civils et les soldats blessés au combat. La maîtrise des hémorragies et le remplacement du volume sanguin par perfusion intraveineuse demeurent essentiels pour le traitement initial des traumatismes. Les pratiques militaires actuelles de réanimation, à savoir la perfusion de solutions salines diluées pour compenser les pertes de sang aigües avant les transfusions, ont été adoptées des traitements civils des traumatismes et n'ont pas été revues depuis plus de 30 ans. Les liquides de réanimation conventionnels peuvent aggraver les lésions cellulaires et avoir un effet défavorable sur les issues cliniques.

Méthodologie: Des études chez l'animal et des essais cliniques limités ont établi que les solutions salines hypertoniques sont efficaces pour compenser les pertes de sang par l'augmentation de la volémie, la réduction des inflammations excessives et la réduction/prévention des œdèmes cérébraux. Le poids et le volume des liquides de réanimation que doit porter le médecin sur le champ de bataille (3 L de solution saline normale, pesant 3 kg, pour remplacer 1 L de sang perdu) posent des problèmes particuliers dans le contexte militaire. On n'a toujours pas réussi à mettre au point un liquide de réanimation optimal, qui serait efficace sur le plan clinique tout en conférant un avantage logistique dans des environnements de combat difficiles. De nouveaux liquides de réanimation sont nécessaires pour les soins des premières lignes.

Le PDT de la capacité interopérable de liquides de réanimation en situation de combat (CILRC) a pour but premier d'effectuer un essai collaboratif multicentrique pour démontrer l'efficacité clinique de la réanimation initiale de victimes de lésions traumatiques graves au moyen de petites quantités de solution saline hypertonique. Il vise également à explorer la biopathologie sous-jacente des complications cellulaires liées aux traumatismes qui découlent des différents liquides de réanimation.

Résultats: Plus de 2 000 patients ont été recrutés dans l'essai sur une période de 3 ans (de mai 2006 à mai 2009). Parallèlement, RDDC a analysé plus de 500 échantillons biologiques prélevés sur 120 patients (pour > 1 million éléments de données) en vue du dosage des biomarqueurs. Un conseil indépendant de sécurité et de surveillance des données a mis fin à l'essai plus tôt que prévu après avoir déterminé que le recrutement de patients supplémentaires n'aurait aucune influence statistique sur les résultats de l'étude. Les observations cliniques de l'essai montrent que les liquides de réanimation hypertoniques ne présentaient aucun avantage par rapport aux solutions salines normales, tant dans la cohorte de l'état de choc (survie après 28 jours) que dans celle des traumatismes cérébraux (fonction neurologique après 6 mois). En d'autres mots, les solutions salines hypertoniques ne sont ni meilleures ni pires que les solutions salines normales à titre de liquide de réanimation, tel qu'indiqué par les résultats cliniques observables.

Importance: Dans l'ensemble, le PDT de la CILRC a atteint ses objectifs. Plus spécifiquement, le projet a démontré : 1) l'avantage logistique potentiel des solutions salines hypertoniques, qui nécessitent 10 % moins de volume de liquide que les solutions salines normales pour obtenir le même résultat clinique, à savoir la réanimation des victimes d'état de choc et de traumatismes cérébraux en situation de combat; 2) la capacité des solutions salines hypertoniques, appuyée sur des données de laboratoire, d'éliminer les réponses inflammatoires excessives, ce qui présente un avantage pour les survivants; 3) la capacité de RDDC d'effectuer, en partenariat avec d'importants organismes de financement externes, des essais cliniques translationnels chez l'humain pouvant aider à répondre aux besoins opérationnels du Méd C; 4) le rôle de meneur de RDDC dans l'exécution et la promotion de recherches biomédicales de pointe sur les traumatismes et le traitement des blessés.

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1 Introduction

1.1 Project Background

1.1.1 Perspective on Combat Injuries

Understanding the causes of death in modern combat operations is critical to identifying areas for potential intervention [1-3]. Hemorrhagic shock and brain injury are leading causes of preventable death and post-traumatic complications in both civilian and conventional military settings [4, 5]. Historically, one fifth of all injured combatants die in battle [6]; although this number has varied depending on the specific campaign and tactical situation; 20% has been the mean mortality rate among injured combatants in all major conflicts since World War II [7, 8]. Most (70 – 80%) injuries in deployed military forces occur as a result of hostile action. The 20% to 30% of non-combat-related injuries in the deployed forces are known as non-battle injuries and include vehicle crashes, falls, and sports injuries [1, 9]. On the battlefield, almost 90% of the deaths occur before evacuation of the injured to a field hospital (i.e., killed in action, KIA), with massive hemorrhage accounting for 50% of those deaths [4, 10]. Even if the injured combatant survives long enough to be transported to a medical facility, hemorrhage still remains the leading cause of morbidity and late mortality [5]. With most combat deaths taking place before arrival to a hospital, interventions must target the early echelons of care to impact the KIA rate [11]. In current wars, medical doctrine of “essential care in theatre” has been adopted to accommodate the dynamic, nonlinear nature of modern warfare [12]. The basic goals for the first responders are to stop the bleeding and keep the injured person alive long enough to be evacuated for definitive care [13].

Precise data are not available to verify the percentage of casualties who are potentially salvageable, but authorities have estimated this number to be approximately 20% [14-16]. The transition from conventional warfare to the current insurgent mode of warfare has also been associated with significantly increased injury severity and fatality [17]. Those who receive the full force of the highly lethal weaponry used in modern-day combat, suffer a variety of injuries not encountered in civilian practice. In current operational theatres, fully three fourths of these injuries are caused by explosive devices [17], which are designed to cause massive bodily destruction by propelling large numbers of fragments toward the intended victims [8]. Use of roadside improvised explosive devices (IEDs), initiates complex, multi-mechanistic forces on the body from the explosion itself and also by the vehicle translocation or colliding with other objects, resulting in occupant blunt trauma [18, 19]. Recent studies of trauma deaths at a Level I Canadian trauma center, showed that blunt trauma represented 87% of all cases and penetrating injuries were only 13%. Brain injuries were the most frequent cause of death (60%), followed by hemorrhage (15%), and then a combination of both injuries (11%). Multiple organ failure caused 5% of deaths, while 9% were from other causes [20]. Despite the high lethality of modern weaponry, advances in rapid prehospital transportation, personal protective devices, and forward deployed trauma care have been associated with a significant decline in the percentage of combatants killed in action and in the case-fatality rate for current conflicts in Iraq and Afghanistan compared with previous conflicts [21, 22]. However, the corollary of these statistics is that more severely injured patients are now surviving to arrival at treatment facilities, with a resultant increase in the category of died of wounds (DOW) [23].

1.1.2 Conventional Fluid Resuscitation Strategies

Battlefield resuscitation provides the greatest opportunity for reducing mortality and morbidity among potentially salvageable combat casualties [24, 25]. The goals of resuscitation in the face of hypovolemic shock and brain injury are restoring end-organ perfusion and maintaining tissue oxygenation while attempting definitive control of bleeding. Use of recombinant factor VIIa has improved hemorrhage control in the context of brain injury and coagulopathy and increasing the ratio of plasma to red cells during early shock resuscitation has improved survival [26]. However, if not performed properly, resuscitation can exacerbate cellular injury caused by shock and the type of resuscitation fluid used plays an important role in this injury pattern [27]. Despite the enormous burden of disease and number of patients affected by post-injury fluid management strategies, consensus regarding the optimal fluid composition and volume of fluid required is lacking [28, 29]. In general, the Canadian Forces (CF) follow widely accepted Advanced Trauma Life Support guidelines for the overall resuscitation of the patient [30]. In addition, these principles are adapted to the combat environment and the tactical situation that may present itself [11]. Current civilian resuscitation strategies are based on data from the late 1950s. The standard-of-care for resuscitation includes infusion of large volumes of dilute isotonic salt solutions to replace blood loss, typically using normal saline (0.9% sodium chloride, NS) or Lactated Ringer (LR), in quantities 2 – 3 times the estimated blood loss [31]. Although considered “standard”, these isotonic crystalloids have not been well studied in prehospital resuscitation of trauma and have not been shown to be superior to other available solutions [32]. However, the low cost and provider familiarity with these solutions has likely been responsible for their “standard solution” status. While aggressive crystalloid-based resuscitation is effective in restoring blood pressure and initially life-saving, it frequently results in an overload of fluids in the body tissues causing edema and a wide spectrum of adverse complications, such as exacerbated bleeding, coagulopathy and adverse immunoinflammatory responses, which can result in multi-organ dysfunction [24, 33].

1.1.3 Small-Volume Hypertonic Resuscitation Fluids

Hypertonic solutions have long been of interest to military physicians due to the logistical constraints of battlefield medicine [34, 35]. An immediate goal of combat resuscitation technology is the development of limited- or small-volume fluid resuscitation strategies, including permissive hypotension, for the treatment of severe hemorrhage to improve battlefield survival and prevent early and late deleterious sequelae [36, 37]. In particular, considerable animal and human research has demonstrated that resuscitation with hypertonic saline (7.5% NS) solutions, with or without added colloids as plasma volume expanders, offer similar physiologic benefits to conventional crystalloids in hypovolemic patients at less than 1/10 the volume [38]. A 1999 Institute of Medicine report on resuscitation of combat casualties recommended Hypertonic Saline 7.5% sodium chloride plus dextran-70 (HSD) as the optimal resuscitation fluid in that environment [39]. Results of 8 randomized controlled trials conducted from the late 1980’s through the early 1990’s evaluating hypertonic resuscitation of post-traumatic hypovolemic shock showed a trend towards a favourable effect on mortality with hypertonic resuscitation, although statistically significant improvements in overall survival outcome was observed in only one trial [40 - 45]. More recent trials conducted using hypertonic resuscitation in hypovolemic shock patients [46 - 48] and severe TBI patients [49, 50] found survival outcome to be inconsistently improved compared to isotonic crystalloids, but documented trends toward improved six-month survival, reduced total fluid requirements, time spent on a ventilator and risk of acute respiratory distress. All these clinical studies suffer from limitations of variable experimental designs and a lack of statistical power needed to detect potentially small differences between treatment groups.

Despite equivocal evidence for survival benefit of hypertonic resuscitation in published clinical trials of trauma patients, compelling evidence from a growing number of basic laboratory investigations demonstrate that hypertonicity has beneficial immunomodulatory activities, affecting both the innate and adaptive immune responses, preventing excessive post-traumatic cellular activation and minimizing inflammatory organ injury [51, 52]. Conclusions from experimental animal models have begun to translate into successful single-centre clinical trials evaluating the immunomodulatory capacity of hypertonic resuscitation in post-traumatic hemorrhagic shock and TBI patients [46, 47, 53, 54]. In fact, hypertonic fluids are emerging as effective first-line osmotherapeutic agents in patients with severe TBI, by aiding in rapid restoration of cerebral perfusion and control of raised intracranial pressure, thereby limiting secondary brain swelling [55, 56]. These studies have identified hypertonic saline as a potentially useful field resuscitation fluid. However, it remains unclear if hypertonic fluids are more effective than isotonic fluids for improving survival and neurological outcomes in patients [47, 48]. Hence, there is an urgent need for adequately powered, prospective randomized controlled trials to validate alternative hypertonic resuscitation strategies for front-line casualty care. For the military, such findings have important implications toward the development of optimal fluid resuscitation strategies under austere battlefield conditions for stabilization of the combat casualty [57].

1.1.4 The Resuscitation Outcomes Consortium (ROC)

Recognizing the enormous potential benefit of this life-saving measure, Defence Research & Development Canada (DRDC), in association with the United States Army Medical Research & Materiel Command (USAMRMC), assumed a leading role within The Technical Cooperation Program (TTCP) – Technical Panel 12 (Combat Casualty Care), to coordinate the pursuit of an ideal resuscitation fluid for battlefield care. Through a series of workshops held between 2001 and 2004, DRDC convened several panels of subject matter experts to make evidence-based recommendations on the current state of fluid resuscitation and to establish an action plan for the design and implementation of an international multi-centre clinical trial to validate the efficacy of hypertonic fluids for initial resuscitation of combat and civilian casualties [58]. During the same period, DRDC Toronto successfully completed two single-centre “feasibility” trials in patients with shock and TBI [46, 53, 54], demonstrating the potential of hypertonic resuscitation as a “proof-of-concept” for larger multi-centre trials [50]. Members of the Combat Fluid Resuscitation Interoperable Capability (CFRIC) Project Team were also recipients of the 2005 TTCP Scientific Achievement Award in recognition of this work.

These early scientific initiatives helped to facilitate the establishment of the Resuscitation Outcomes Consortium (ROC)[59] – a massive \$50M collaborative network of 10 Regional Clinical Centers (see **Annex A** and *Figure 1*) throughout North America (8 US, 2 Canadian), plus a Data Coordinating Centre (DCC). ROC was sponsored primarily by the National Heart, Lung, & Blood Institute (NHLBI) of the National Institutes of Health (NIH), with joint funding from the NIH’s Institute of Neurological Disorders & Stroke, the Institute of Circulatory & Respiratory Health (ICRH) of the Canadian Institute of Health Research (CIHR), the American Heart Association, the Heart & Stroke Foundation of Canada, USAMRMC and DRDC. With approval of CFRIC TDP in 2004 and subsequent establishment of a Memorandum of Understanding (MOU) with the ICRH, DRDC became a key partner in the ROC. The CFRIC TDP provided funding (\$5M) for the two Canadian trial centres (Sunnybrook/St. Michael’s Hospitals in Toronto; Ottawa Civic/Vancouver’s St. Paul’s Hospitals).

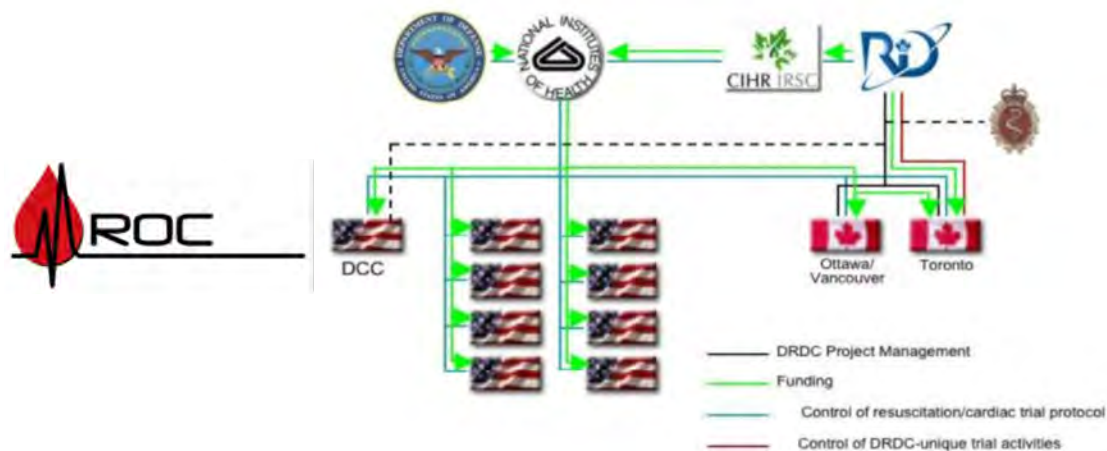


Figure 1: Resuscitation Outcomes Consortium (ROC); involved a network of 10 regional clinical centers and 114 Emergency Medical Services (EMS) agencies across North America, with a target enrollment of >5000 patients

ROC was created to provide infrastructure and project support to conduct multiple outcome-oriented randomized controlled trials in the prehospital setting following life-threatening trauma and cardiopulmonary arrest that will rapidly transfer to evidence-based change in clinical practice [59]. ROC investigators will conduct collaborative trials of variable size and duration, leveraging the combined power of the member institutions and promoting the rapid translation of promising scientific and clinical advances for the public good. Trials may evaluate existing or new therapies, such as novel resuscitation fluids, hemorrhage control strategies, use of neuroprotectants and pharmacologic immune modulators [60].

The first intervention trials from ROC were designed to study the impact of initial hypertonic resuscitation, with and without dextran, on outcomes after life-threatening trauma. This three-arm randomized controlled trial compared the effects of resuscitation with a 250-ml infusion of 7.5% hypertonic saline (HS) or HSD vs. standard NS, on outcomes in the two patient populations: those with hypovolemic shock (blood pressure ≤ 70 mmHg) and those with severe traumatic brain injury (Glasgow Coma Scale score ≤ 8). The randomization scheme for the groups was 1:1:2 to optimize power (set at 80%) to test the hypothesis of the active treatment arms (HSD or HS) vs. a common control (NS). During a three-year period, 5,848 patients (i.e., 3,726 Shock patients; 2,122 TBI patients) were to be randomized, with a primary end point of twenty-eight-day survival in the Shock cohort and six-month neurologic outcomes in the TBI cohort [61]. In parallel, three trial centres (Toronto, San Diego, Seattle) conducted an ancillary “inflammatory markers” study in a subgroup of ROC patients, designed to investigate the potential immunomodulatory capacity of hypertonic fluids.

1.1.5 Subject Recruitment and Informed Consent

This study qualified for the “Exception from informed consent required for emergency research” outlined in Food and Drug Administration (FDA) regulation 21CFR50.24. Specifics of this regulation include subjects in a life-threatening situation, inability to give informed consent because of their medical condition, an intervention that must be administered before consent from a legally authorized representative is feasible, inability to prospectively identify individuals likely

to become eligible for participation in the trial, prospect of direct benefit to enrolled subjects, inability to conduct the investigation without the waiver, and ongoing attempts to contact the legally authorized representative. Inclusion of patients in this study was done with waiver of consent and option to withdraw at any time included in the notification sent to both patient and family. Justification to forego informed consent has been provided according to all criteria set forth by the Tri-Council Agreement for research in emergency health situations (Article 2.8). Each of the ROC Canadian sites had in place notification processes approved according to hospital Research Ethics Board standards. This protocol was approved by the DRDC Human Research Ethics Committee.

1.1.6 Preliminary Results from ROC

Patient enrollment began on May 9, 2006 and ended on May 4, 2009. During this three-year period, the trial enrolled a total of 2,184 patients (853 Shock patients and 1,331 TBI patients). Concurrently, DRDC analyzed over 500 biological samples obtained from 120 patients (generating > 1 million data points) for determination of cellular and molecular inflammatory markers. An independent Data Safety and Monitoring Board (DSMB) stopped the Shock arm of the trial ahead of schedule (~23% of proposed sample size) on the basis of statistical futility and potential safety concerns. Clinical findings from the Shock cohort showed no differences in twenty-eight-day survival between the treatment groups: HSD 74.5%, HS 72.9%, NS 74.3% ($p = 0.90$); despite an apparent trend towards higher early mortality (up to 6 hours) in the hypertonic groups. Despite the absence of safety concerns, the TBI arm was terminated early (~63% of planned enrollment) by DSMB as it met pre-specified futility criteria. Results from this cohort showed no difference in twenty-eight-day survival: HSD 75.1%, HS 76.5%, NS 75.1%, ($p = 0.88$); or six-month neurologic outcomes: HSD 59.9%, HS 58.4%, NS 56.1% ($p = 0.5$). The main conclusion from both cohorts was that prehospital hypertonic fluids conveyed no survival or neurologic outcome advantages. Analyses of the inflammatory markers are ongoing, but preliminary results suggest a beneficial pattern of immunomodulation by hypertonic fluids.

2 CFRIC TDP Performance

2.1 Technical Performance Summary

The overall objective of the CFRIC TDP was to demonstrate the capacity of small-volume hypertonic saline solutions for prehospital resuscitation of severely injured trauma patients, permitting regulatory approval and adoption for front-line casualty care by the CF. This was achieved by participation in the large multi-centre ROC trial (*Table 1*).

Table 1: Key Objectives of the CFRIC TDP

Key Objectives	Achieved
No. 1 - Validate the clinical efficacy of small-volume resuscitation using HS vs. HSD vs. NS in patients suffering from Shock or TBI using a large randomized control trial.	√
No. 2 - Seek regulatory approval for hypertonic saline, which will promote evidence-based revision of standard-of-care for combat resuscitation, that has not changed in over 30 years.	√
No. 3 - Integrate and translate knowledge of inflammatory organ dysfunction through measurement of cellular injury markers to mitigate disability risk.	√
No. 4 - Improve far-forward medical logistics under austere battlefield conditions through reduced fluid volume, increased agility, and greater interoperability between allied forces.	√

2.1.1 Project Objectives

Objective No. 1

Result: *Partial Success*

Validate the clinical superiority of small-volume resuscitation using HS vs. HSD vs. NS in patients suffering from Shock or TBI using a large randomized control trial.

Achievements:

The main objective of CFRIC TDP and the ROC was to complete a clinical trial large enough to provide adequate statistical power to demonstrate definitively, whether or not hypertonic saline solutions are in fact superior, in terms of patient survival and neurological outcome of trauma patients, to the current standard-of-care normal saline when administered in the prehospital setting.

ROC patient enrolment began on May 9, 2006 and ended on May 4, 2009. During this three-year period, the trial enrolled a total of 2,184 patients (853 Shock patients and 1,331 TBI patients) making it the largest randomized controlled trial ever to evaluate hypertonic saline for resuscitation of traumatic injury. However, to be considered fully successful on this objective, the ROC trial would have needed to continue long enough to enroll its combined target sample size of 5,848 patients (i.e., 3,726 Shock patients; 2,122 TBI patients) in order to allow valid statistical comparisons between the treatment groups.

The results show that for the Shock arm, twenty-eight-day mortality was no different with hypertonic saline alone or with dextran vs. normal saline. The DSMB recommended early termination of the trial based on analyses of the interim data showing that deaths occurred earlier

in the hypertonic saline groups, despite similar cumulative twenty-eight-day mortality between the hypertonic and normal saline groups.

In the hypertonic saline for the TBI arm, analyses of six-month follow-up data do not suggest a similar trend toward earlier deaths in the hypertonic saline vs. normal saline group. Further analyses are underway, with publication anticipated in a peer-reviewed scientific journal.

The primary reasons for the partial success of this objective are the result of multiple regulatory delays/suspensions of the ROC trial and the early final closure of the study (*Table 2*).

Table 2: Overview of Regulatory Delays and Suspensions

Suspension	Date	Duration	Reason(s)	Recommendations
Voluntary enrollment suspension	01/05/2005	2 month	Concern over potential risk of anaphylaxis related to dextran colloids in patients.	Based on data from > 900 trauma patients enrolled in clinical trials receiving HSD & >20,000 patients receiving Rescuflow in clinical use, no reports of dextran-related anaphylaxis, the risk from dextran was remote.
Voluntary Enrollment suspension	10/26/2006	1 month	Concerns related to potential variations in in-hospital treatment (after intervention).	FDA recommended that all participating sites need to monitor serum sodium every 6 h for the first 24 h; provide oversight of the ICU staff to ensure adherence to practice guidelines; provide Level 1 trauma care 24/7.
FDA-imposed suspension	07/31/2008	9 month	Concerns related to consent in US trial centres	FDA temp suspended the Inflammatory Markers ancillary study; re-approved collection of blood samples for biomarker analyses Mar 27, 2009.
Voluntary enrollment suspension	08/28/2008	3 month	DSMB recommended suspension of enrollment of hypotensive patients in to the shock cohort; enrolment of shock patients was stopped in March, 2009.	On recommendation of DSMB and FDA enrollment into the Shock cohort was voluntarily suspended in Aug, 2008. Suspension of the TBI study was also implemented to allow retraining of EMS providers to enroll only TBI patients. Resumption of ROC clinical trial with exclusive enrollment of TBI patients, and exclusion of shock patients was re-approved by FDA on Nov 14, 2008.
Trial Terminated	05/04/2009	Final	DSMB recommended stopping enrollment on the basis of planned interim analysis of data from 1073 TBI patients who were followed for 6 m. This analysis suggested hypertonic saline solutions offered no benefit over normal saline, nor was there any difference in risks between the 2 treatments.	Based on the conclusion that further patient enrolment would not change the trial outcome, the FDA accepted the recommendation that the ROC trial be terminated, effective 4 May 2009.

Note: FDA implies US Food and Drug Administration; ICU implies Intensive Care Unit

Despite the fact that the ROC trial was stopped early (at about half of the total planned enrollment) on the basis of interim statistical futility (i.e., it implies that there is little hope of achieving study objectives with the planned sample size), the fact that hypertonic fluids were found to be no more harmful than standard fluid treatments has important implications for the military. From a military operational medicine perspective, the equivalent therapeutic efficacy of

hypertonic fluids at < 10% the fluid volume of normal saline required for similar clinical outcome confers a substantial logistical advantage.

For the Shock cohort, the study was a one-sided trial for superiority, involving three arms, and a traditional significance level of 0.025 is divided by 2. The most efficient randomization distribution for testing differences between two treatments to a common control is 1:1:2 and was used in this study. The study was powered to detect a 4.8% overall difference in survival (from 64.6% to 69.4%) between the control group, NS, and at least one of the two treatment groups, HS or HSD, with an overall power of 80% (62.6% power for an individual agent). Based on these calculations, a total of 3,726 patients was required, with 1,092 patients in each hypertonic saline arm and 1,542 patients in the control arm NS. Feasibility of this study was assessed using anticipated enrollment from each ROC site. Based on an estimated total annual enrollment of 1,280 patients, the anticipated length of this trial with this sample size was to be approximately three and a half years.

Primary outcomes for TBI patients include neurologic function at six months after injury based on the extended Glasgow Outcome Scale score. A 15% relative reduction in prevalence of poor outcomes was considered to be clinically relevant. After a similar sample calculation as for the shock cohort, estimating a 49% incidence of poor outcomes, and assuming that hypertonic fluids offer a relative 15% reduction in risk of poor outcomes, 1,688 patients are required to detect this difference, with an overall power of 80%. Using the most efficient randomization distribution of 1:1:2, there were to be 494 patients in each hypertonic saline group and 699 control patients. To account for uninjured patients in the analysis, the sample size was adjusted to 2,122 patients. Similar to the hypovolemic shock cohort, feasibility was assessed based on anticipated enrollment from each ROC site. The anticipated length of this trial with this sample size was approximately one and a half years for study enrollment and approximately two years to collect primary outcomes at six months of follow-up [61].

Aggressive futility monitoring of Phase III trials using a suitable intermediate endpoint may substantially increase the probability of stopping early when they would not have shown a statistically significant treatment effect had they gone on to completion [62]. A futility-stopping rule can drastically reduce the time and money spent on clinical trials, and can more rapidly find effective treatments. On the other hand, early stopping similarly jeopardizes analyses of secondary outcomes, which may be pivotal in clinical decisions when there is truly no survival effect. Data related to adverse events are limited, and subgroup analyses thwarted [63].

Objective No. 2

Result: *Full Success*

Seek regulatory approval for hypertonic saline, which will promote evidence-based revision of standard-of-care for combat resuscitation that has not changed in over 50 years.

Achievements:

Regulatory approval of 7.5% hypertonic saline alone or admixed with dextran-70 is a key objective of both the CFRIC TDP and the ROC study. Hypertonic saline with dextran (Rescueflow[®] marketed by Biophausia AB, Uppsala, Sweden) has achieved regulatory approval for use in at least 14 European countries [64], but has not been granted approval by FDA or Health Canada for the resuscitation of trauma patients in North America [35].

Hypertonic fluids administered to patients in the ROC study were used under an Investigational New Drug application submitted and reviewed by the FDA Center for Biologics Evaluation and Research and Office of Blood Research and Review. The FDA also reviewed the plan for community notification and consultation proposed by each US site. A similar Investigational New Drug process (Clinical Trial Agreement) was required for use of HS and HSD at the Canadian sites. Health Canada reviewed the initial protocol and manufacturing information and granted approval within 30 days.

Led by CF Health Services Regulatory Affairs group, DRDC and the USAMRMC are working cooperatively to obtain regulatory approval by Health Canada and the FDA for use of hypertonic resuscitation fluids as treatments for hemorrhagic hypotension and TBI, following penetrating or blunt trauma for acute medical care during combat and civilian emergency situations. It is recognized that no treatment is without risk, but there are some significant benefits derived from the use of small volume solutions for full or limited resuscitation, especially in austere prehospital settings. HS and HSD type solutions have primary benefit as the initial resuscitation solution by rapidly expanding plasma volume and improving hemodynamics, thereby extending the therapeutic window until the patient can be transported to a definitive treatment centre. Validation and adoption of CFRIC TDP technology would facilitate significant doctrinal change within Military Operational Medicine.

Objective No. 3

Result: *Full Success*

Integrate and translate knowledge of inflammatory organ dysfunction through measurement of cellular and molecular injury markers to mitigate disability risk.

Achievements:

The rationale for testing hypertonic saline in these trials was that compared with normal saline, hypertonic solutions had been shown to improve tissue perfusion and reduce the excessive inflammatory response early after injury, which results in organ damage [46, 47]. These fluids may be particularly beneficial for patients with TBI, as they maintain cerebral perfusion while reducing intracranial swelling [53, 54].

In addition to the primary survival outcome examined by the main ROC trial, a significant objective of the CFRIC TDP was to study the cellular and molecular injury marker profile in a subset of patients resuscitated with hypertonic saline vs. normal saline. DRDC Toronto has taken a leading role in the design and implementation of an ancillary laboratory study, and provided expertise in developing sensitive cellular and molecular assays to measure specific injury markers, which were adopted by the ROC inflammatory markers group.

In all, this study collected and analyzed over 500 biological samples from 120 patients enrolled into the ROC trial. These analyses involved cutting-edge integrative molecular and cellular biomedical research techniques pioneered by DRDC Toronto, to provide a comprehensive examination of the immunoinflammatory response (generating > 1 million individual data points) in resuscitated patients.

The CFRIC TDP also benefited as essential collaborators in an NIH R01 (No. GM076101-01A1) research grant (\$1M) awarded to ROC 'Inflammatory Markers' subgroup; this funding has been used to leverage costs associated with laboratory assays and allow for a larger patient sample size.

A key challenge of the CFRIC TDP was to establish an international applied research network, requiring the integration of multiple hospital and laboratory teams from 5 institutions to respond to on-call patient samples on a 24-hour per day / 7-day per week basis. Samples of peripheral blood were collected upon emergency department arrival, 12-hour, 24-hour and 7-days after treatment, by a dedicated team of hospital-based phlebotomists and research nurses [50]. Samples were immediately shipped to DRDC Toronto for processing within 3-hour by a highly trained team of laboratory technologists following standardized operating protocols, using sophisticated flow cytometric cellular and soluble proteomic analyses of selected immunoinflammatory markers.

Preliminary findings from the inflammatory markers substudy were presented at the *33rd Annual Shock Society Conference* in June 2010 [65 - 67] and at the *Advanced Technology Applications for Combat Casualty Care (ATACCC) Conference* in August, 2010 [68]; additional papers have been accepted for presentation at the *Trauma Association of Canada Annual Scientific Meeting* [69 - 71]. Several manuscripts are in preparation for submission for publication in peer-reviewed scientific journals. These preliminary results suggest a favourable pattern of immunomodulation by hypertonic fluids in those subgroups of trauma patients most at risk from the consequences of hyperinflammatory states, and therefore, may derive the greatest benefit from them.

The CFRIC TDP deliverables are expected to provide a greater understanding of the biological mechanisms that regulate the anti-inflammatory and immunological effects of hypertonic fluids in humans during shock and TBI states, contributing to the early diagnosis of inflammatory organ dysfunction. Additionally, the scientific and clinical advances arising from the CFRIC TDP will provide the basis to guide future mechanism-driven trials, where therapies are targeted at patients with definitive evidence of a pathophysiologic process.

Overall, publication of the CFRIC TDP findings in the peer-reviewed literature will facilitate translation of clinical and laboratory data into revision of standards and redefinition CF medical doctrine [72-73].

Objective No. 4

Result: *Full Success*

Improve far-forward Medical logistics under austere battlefield conditions through reduced fluid volume, increased agility, and greater interoperability between allied forces.

Achievements:

An important objective of CFRIC TDP is to provide transformational technologies to improve military medical logistics in support of operational/deployed forces. As such, an optimal resuscitation fluid, that is at once portable, yet clinically effective in austere combat settings with long transport times is highly desirable.

Unique challenges for military medical care include complex tactical situations and the logistic limitations of weight and cube under far-forward conditions. A 1-litre bag of conventional isotonic crystalloid fluid weighs 1 kg, which limits the amount of fluid easily carried onto the battlefield.

Hypertonic fluids can provide similar physiological and clinical effects, while also optimizing the inflammatory response at one-tenth to one-twelfth the volume of conventional crystalloids. This multi-fold reduction in equipment weight is clearly of logistical benefit to military medics, enabling them to carry the smallest volume and weight of resuscitation fluid.

2.2 Schedule Performance Summary

Table 3 indicates the original, baseline project schedule for completing major project milestones and compares it to schedule revisions made during the course of the project and the resulting schedule variance.

Table 3: Major Project Milestones

CFRIC TDP Milestone	Planned Finish	Actual Finish	Variance (mos.)
Project Definition Phase			
Project Approval	March, 2004	February, 2004	0
Level-1 MOU/PA signed with CIHR	March, 2005	May, 2005	+2
Project Execution Phase			
Experimental Protocols Established	March, 2005	May, 2005	+2
Contracts Prepared (RFP/SOW/Sole Source)	April, 2005	April, 2005	0
Contract Awarded to Sunnybrook Hosp. (\$1M)	April, 2005	May, 2006	+13
Exploitation Plan Developed	June, 2005	June, 2005	0
Major Equipment Purchased	July, 2005	July, 2005	0
Pilot Trials and Personnel Training	July, 2005	December, 2005	+5
Lab Assays Validated	August, 2005	January, 2006	+5
ROC Clinical Trials Begin	September, 2005	July, 2006	+10
ROC Clinical Trials End	April, 2009	May, 2009	+1
Data Analysis	December, 2008	January, 2010	+13
Project Close-out Phase			
Final SRB	February, 2009	June, 2010	+16
Project Completion Report	March, 2009	June, 2010	+15
Archive Documentation	March, 2009	July, 2010	+16
Follow-on Activities			
Fluid Resuscitation Symposium	June, 2009	October, 2010	+16
Publication of Clinical & Laboratory Findings	July, 2010	January, 2011	+18
Regulatory Approvals (FDA/Health CAN)	January, 2009	January, 2011	+12
CF Implementation	Post Approval	Post Approval	

2.2.1 Schedule Variances

- The CFRIC TDP was implemented on schedule with major contracts prepared and submitted to public works 6 months in advance of the projected requirements. However, a protracted security clearance process (> 13 months) by Public Works and Government Services Canada and their Departmental Security Office (PWGSC/D-Secur) delayed the awarding of major contracts.
- The start of patient enrolment into ROC Trial was initially delayed by 10 months and further postponed by an additional 8 months due to periodic regulatory delays/suspensions imposed externally by the NIH and/or DSMB, as outline above.
- Overall, the CFRIC TDP was re-scoped to end March 2010 to allow time for additional patient enrolment and completion of clinical and laboratory data analyses.

2.3 Cost Performance Summary

The CFRIC TDP officially began in April 2005 and was originally scheduled to end March 2009. However, the project was granted extension until March 2010 because the launch of the ROC trial was delayed by 8 months and it also experienced several FDA-imposed regulatory delays. The original CFRIC TDP funding allocation was \$5M, but termination of the ROC trial 1-year ahead of schedule resulted in a reduction in total costs and a return of \$1.1M.

The original, approved, **baseline budget** for this project was \$4,994,000 plus a 10% contingency as indicated in *Table 4* below.

Table 4: The CFRIC TDP Baseline Budget

Cost Category	2004-05	2005-06	2006-07	2007-08	2008-09	2009-10	Subtotals
Contribution to CIHR	0	600,000	600,000	400,000	400,000		2,000,000
Contracts	0	250,000	300,000	300,000	150,000		1,000,000
Reagents/Consumables	0	300,000	250,000	200,000	100,000		850,000
Equipment	10,000	375,000	0	0	0		385,000
Equipment Service	0	30,000	50,000	50,000	50,000		180,000
Meetings/Workshops	0	0	50,000	0	50,000		100,000
Training	0	10,000	6,000	0	0		16,000
Specimen Delivery	0	10,000	10,000	10,000	0		30,000
Travel	28,000	50,000	45,000	45,000	45,000		213,000
Project Mgt (G&A)	30,000	50,000	50,000	45,000	45,000		220,000
Annual Totals	68,000	1,675,000	1,361,000	1,050,000	840,000		4,994,000
					Contingency		499,400.0
					Total		5,493,400

During the course of project execution, variances occurred between the baseline budget and actual expenditures derived from the Financial Management and Analysis Sector (FMAS-derived) as shown below in *Table 5*.

Table 5: The CFRIC TDP Actual Expenditures

	Past Actual Spending (FMAS)						Projected	Projected
	2004-05	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	Total
Baseline	\$ 68,000	\$1,675,000	\$1,361,000	\$1,050,000	\$ 840,000	\$ -	\$ -	\$4,994,000
Actual	\$ 108,503	\$1,038,883	\$1,167,786	\$ 641,076	\$ 723,000	\$ 120,000	\$ 40,000	\$3,839,248
Delta	\$ (40,503)	\$ 636,117	\$ 193,214	\$ 408,924	\$ 117,000	\$(120,000)	\$ (40,000)	\$1,154,752

Changes in the baseline project schedule resulted in the project being extended first into FY 2009 - 2010 to allow further patient enrolment and again into FY 2010 - 2011 to facilitate CFRIC exploitation. Thus, the original baseline budget was adjusted for actual annual expenses and an estimate of expenditures for FY 2009 - 2010 of approximately \$120,000 and FY 2010 – 2011 as shown in *Figure 2*.

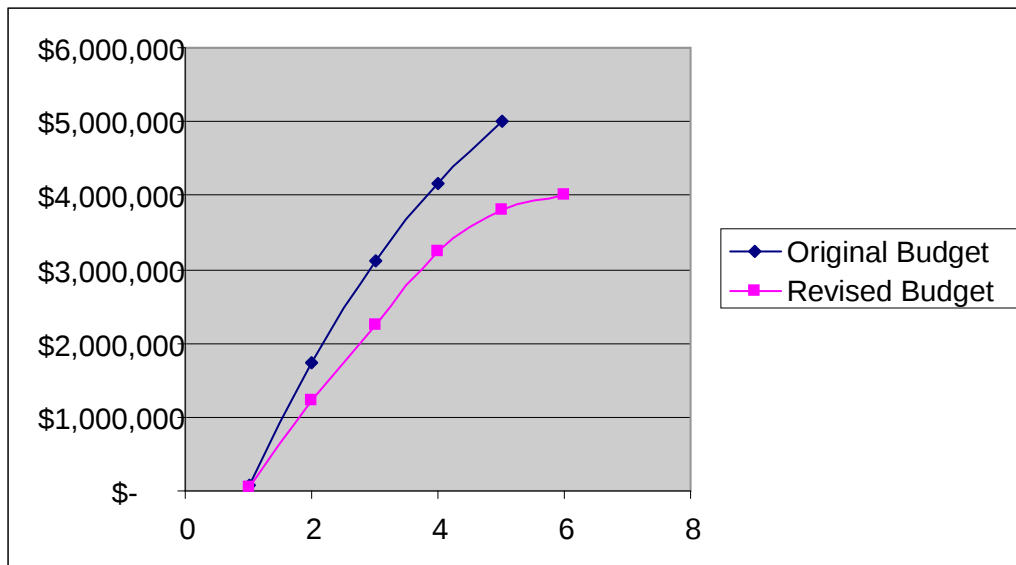


Figure 2: Adjustment of Original Baseline Budget

3 Recommendation for Follow-on Activity

3.1 Transition of the CFRIC TDP into Operations

- The CF Surgeon General has agreed to exploit the outcome of the ROC hypertonic fluid resuscitation trial. Full exploitation by the CF hinges on receiving Health Canada approval and securing a commercial source of hypertonic fluid supply.
- Led by the CF Health Services Regulatory Affairs group, DRDC will help to facilitate the collaboration with DoD in submitting required trial data and documentation to Health Canada for regulatory approval.
- Hypertonic solutions have been produced and supplied by a European manufacturer for the ROC trial and also for off-label use by CF Health Services. In cooperation with DoD (a high-volume purchaser of hypertonic solutions), DRDC will help CF Health Services to negotiate a guaranteed supply of hypertonic fluids for use by the CF.

3.2 Follow-on Research and Development Projects

- The CFRIC TDP has provided the foundation for future human clinical trials that may be of high priority to the Canadian military. Working through the CFRIC TDP, DRDC Toronto has developed strong collaborative research links with the major academic/hospital-based trauma and critical care programs that promote the transition of bench research to the translational level. A key area of research success that distinguishes DRDC Toronto from our sister laboratories is the ability to conduct human translational clinical research, which has very high and immediate relevance to the CF Health Services and the Surgeon General.
- DRDC Toronto has taken a leading role amongst our international allies and collaborators in the area of post-traumatic immune-inflammatory research; such bio-molecular studies are at the forefront of modern trauma and combat casualty care investigation.
- Beyond hypertonic fluid resuscitation the ROC has interest in conducting future clinical trials to evaluate traumatic coagulopathy and damage control resuscitation utilizing the concept of hemostatic resuscitation, by administering plasma, platelets and red blood cells at a ratio of 1:1:1. Additionally, it showed limit the excessive use of packed red blood cells and crystalloids to prevent dilutional coagulopathy. Such a strategy is of primary importance to CF Operational Medicine.

3.3 Intellectual Property Management

- The CFRIC TDP is not anticipated to result in any commercial products. The work accomplished under the CFRIC TDP, including all deliverables and Intellectual Property rights, is owned by the Canada Government.

3.4 Disposition on Project Products

- All equipment acquired during this TDP will be retained by DRDC Toronto and used in support of current and future projects.

4 Lesson Learned Summary

The primary lessons learned from this CFRIC TDP include: (1) the absolute necessity to initiate major contracts requiring DRDC security clearance at least 1-year in advance; (2) advantages of preparing inter-agency MOUs to facilitate funding transfers; and (3) challenges associated with implementing a 24/7 on-call laboratory sample processing schedule.

4.1 Contracting/Procurement

- Recognizing the potential for delays and the substantial work associated with implementing multiple contracts in support of any given project, efforts were made from the early planning stages to minimize the number of contracts required to implement the CFRIC TDP.
- The primary contractual requirements were to provide support for the two designated ROC sites in Toronto (i.e., Sunnybrook and St. Michael's Hospitals) to cover costs associated with patient enrolment, blood collection and sample shipment to DRDC Toronto. Therefore, a single statement of work (SOW) and Request for Proposals (RFP) were prepared in the amount not to exceed \$1M. At the time, the recommended procurement strategy was one of Sole Source.
- Chronology of CFRIC Contract No. W7711-05-7955 (Sunnybrook Hospital, C\$950K) (*Table 6*):
 - ♦ Contract SOW and request for Security Requirement Check List (SRCL) were submitted April 1, 2005 for local approval at DRDC Toronto.
 - ♦ SRCL was forwarded to PWGSC/D-Secur in June 2005.
 - ♦ The RFP with the SRCL was sent to the contractor by PWGSC on July 22, 2005.
 - ♦ Despite repeated inquiries there was no information provided by D-Secur regarding the status of the clearance process up to December, 2005.
 - ♦ Following direct enquiry by the Project Director to D-Secur January 25, 2006 expressing our concern for how long the process was taking we received our Security Clearance for Sunnybrook Hospital in March 2006,
 - ♦ After which it took about additional 3 months for the Canadian and International Industrial Security Directorate of PWGSC to finalize the contract, which was officially awarded in May 2006.
 - ♦ This protracted security clearance process (> 13 months) impacted hiring of required personnel to coordinate the initiation of the clinical research project for the July 2006 start date.

Table 6: Contractual Timeline Summary

Contract Value	SOW		SRCL	Requisition	RFP	Proposals	Contract
	Development	Approval	Approval	Approval	Release	Evaluation	Award
\$950K	1 month	3 months	12 months	2 months	NA	NA	14 months

- In general, the procurement process for the CFRIC project was satisfactory. A dedicated budget and coding were in place, but some stumbling blocks arose in some instances. For

example, although reagents used for flow cytometry were readily available they were also expensive. Two vials often exceeded the DRDC \$1K Sole Source limit, and since standing offers (SOs) were not in place for all required companies, several reagents could not be easily ordered. Technical members were required to find and request quotes for similar reagents that would never be ordered, but merely quoted to satisfy Sole Source requirements. This was deemed to be very time consuming and very frustrating. Moving forward, it is recommended that SOs should be set in place for the duration of projects (e.g., 3 - 5 years) to avoid annual “option to extend” requests from vendors, which create administrative paper work. Tighter control of regional SOs is essential to avoid “lapse in service” penalties. Similarly, advance planning must be improved to avoid redundant procurement, resource expiration, and down-time if a project is delayed or postponed. A designated project team member should be solely responsible for administering requisition forms and the receipt-of-product.

4.2 Laboratory Data Collection Team

- One of the greatest challenges and accomplishments of the CFRIC TDP was the establishment of a 24/7 on-call laboratory research team, comprised of indeterminate DRDC Toronto employees, external contractors, and graduate students. Given the difficulties associated with conducting human translational biomedical research trials and particularly the inherent unpredictability of traumatic injury studies, it was necessary to assemble a network of more than 20 highly skilled medical, scientific, and technical personnel to ensure the maximal accrual of Shock and TBI patients into the ROC inflammatory markers study. This undertaking required extensive preparation of standardized operating protocols and cross-training between personnel located across Canada and the US (i.e., Toronto, Seattle and Boston) to ensure the reproducibility between biological samples processed in different laboratories.
- Standby scheduling allowed for 24/7 coverage, and procedures for receiving samples at all hours (i.e., the use of a taxi service, the reception of samples by Commissionaires) proved successful; however, on occasion, technical members and the CFRIC TDP contractors could not arrive to process samples when scheduled. During other instances, technical team members arrived as scheduled but were unable to process samples effectively.
- During the CFRIC TDP, DRDC Toronto security policy requires that contract staff must be accompanied by a full-time employee when on-site after hours; consequently DRDC employees were required to be on call solely to escort contractors while sample processing was completed. This increased the manpower and costs associated with the project. It is recommended that technical members and the CFRIC TDP contractors should adhere to schedules and technical members on standby duty should be properly trained about all processing duties and responsibilities to be most effective.
- Additional in-house research projects carried out concurrently with the CFRIC TDP allowed staff to effectively cross-train for related projects, but also challenged technical members when required to receive and process samples that arrived during regular working hours. On occasion, technical members felt pressured to ensure that no CFRIC TDP samples were lost at any cost. It is recommended for future studies that technical members be engaged in all planning sessions and be primarily responsible for sample processing during the day, while contract staff (if required) be responsible for processing samples that arrive outside regular hours via an on-call duty schedule. Implementing this would ensure that trained contractors deal with all samples, and would limit cost associated with full-time staff being on standby and call-back duties.

- There was also concern that in specific instances, the delineation between the duties and responsibilities of the CFRIC TDP contract staff as compared to technical members became blurred. As part of their ongoing training and skills development, contractors also provided support to non-CFRIC studies, which may have been perceived as over-extending their planning and decision-making authority. It is recommended that for future projects requiring significant placement of contractors within DRDC, the roles and responsibilities of on-site contractors and access to any amenities deemed essential need to be properly documented in the contract. All project team members should be updated regularly and engaged to provide input and feedback under the leadership of the project manager.
- In light of the challenges the CFRIC TDP has experienced in engaging on-site contractor services noted above, alternative arrangements must be taken into considerations to address administrative, logistical and technical issues of any required on-site external service, during the early planning stage of a major proposed project. This can best be achieved by a project team consisting of members from the management, scientific, technical and corporate streams

4.3 Experimental Protocols, Training, and Equipment

- Equipment resources and generous space allocation were appropriate for the team members to carry out their required work. Time sensitive assays with multiple time points to complete within a working day had the potential to become quite confusing. However, designating team members to focus on one or two portions of the sample processing during those periods when a second major project was running concurrently meant that all team members could efficiently assimilate and process the samples. Coordinating the use of centrifuges was challenging at times because the inherent steps of running multiple assays involving centrifugation often overlapped.
- The help of contractors was required given the scale of the work involved in the CFRIC TDP project; however, some technical members felt that too much emphasis was placed on the contractors that may have limited in-house capability development. For example, some ad-hoc training was carried out on the operation of the cytometers, but no formal training was provided to enable technical members to become proficient user of this equipment. Cytometer availability was not an issue when concurrent studies requiring the same instrumentation were running. Ongoing succession planning and capability development warrant that time should be embedded into projects for technical training.

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List of Acronyms

CF	Canadian Forces
CFHS	Canadian Forces Health Services
CFRIC	Combat Fluid Resuscitation Interoperable Capability
CIHR	Canadian Institutes of Health Research
DCC	Data Coordinating Center
DoD	Department of Defense
DOW	Died of Wounds
DRDC	Defence Research & Development Canada
D-Secur	Departmental Security Office
DSMB	Data Safety and Monitoring Board
EMS	Emergency Medical Services
FDA	United States Food and Drug Administration
FMAS	Financial Management and Analysis Sector
HS	Hypertonic Saline, 7.5% sodium chloride
HSD	Hypertonic Saline 7.5% sodium chloride + dextran-70
ICU	Intensive Care Unit
ICRH	Institute of Circulatory & Respiratory Health
IED	Improvised Explosive Device
KIA	Killed in Action
LR	Lactated Ringer
MOU	Memorandum of Understanding
NHLBI	National Heart, Lung & Blood Institute
NIH	National Institutes of Health
NS	Normal Saline, 0.9% sodium chloride
PWGSC	Public Works and Government Services Canada
RFP	Request for Proposals
ROC	Resuscitation Outcomes Consortium
SRB	Senior Review Board
SRCL	Security Requirement Check List
SOs	Standing Offers
SOW	Statement of Work
TBI	Traumatic Brain Injury
TDP	Technology Demonstration Program

TTCP	The Technical Cooperation Program
US	United States
USAMRMC	United States Army Medical Research & Material Command

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Annex A ROC Regional Clinical Centers

Regional Clinical Centers Participating in the Resuscitation Outcomes Consortium



The ROC consists of EMS systems and hospitals in the cities or regions listed below.

- Alabama Resuscitation Center, involving systems in Central and possibly Northern Alabama: Tom Terndrup, MD, Principal Investigator
- Dallas, TX (includes some surrounding cities): Ahamed Idris, MD, Principal Investigator • Iowa City, IA (includes 10 cities throughout Iowa): Richard Kerber, MD, Principal Investigator
- Milwaukee, WI: Tom Aufderheide, MD, Principal Investigator
- Pittsburgh, PA (includes some suburbs): Clif Callaway, MD, Principal Investigator
- Portland, OR (includes 4 counties): Jerris Hedges, MD, Principal Investigator
- Ottawa, Ontario /Vancouver, BC (includes 20 other cities in the OPALS group): Ian Stiell, MD, Principal Investigator, Jim Christenson, MD, Co-Principal Investigator in Vancouver BC
- San Diego, CA (includes the entire county): Dave Hoyt, MD, Principal Investigator
- Seattle/King County, WA: Peter Kudenchuk, MD, Principal Investigator
- Toronto, Ontario (includes surrounding areas): Art Slutsky, MD, Principal Investigator, Laurie Morrison, MD and Paul Dorian, MD, Co-Principal Investigators.

The Study Chair is Myron L. Weisfeldt, MD, Chair of Medicine at Johns Hopkins; the co-chair for cardiac arrest is Joseph Ornato, MD, Head of the Emergency Medicine Department at the Medical College of Virginia.

The Clinical and Data Coordinating Center is located at the University of Washington, Seattle, WA under the direction of Gerald van Belle, PhD and Graham Nichol, MD.

The Ethics Officer is Jeremy Sugarman, MD, MPH, MA, Berman Bioethics Institute, Johns Hopkins University.

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(U) This project evaluated novel small-volume hypertonic fluids for combat resuscitation for improvement in patient survivability and reduction of the post-traumatic inflammatory response, and for reducing overall fluid volume requirements. The outcome has demonstrated that there is no clinically significant difference in resuscitating shock and traumatic brain injury (TBI) patients with either normal or hypertonic saline. However, from a military operational medical care perspective, the less than 10% hypertonic fluid volume (versus normal saline volume) required to generate the same clinical outcome confers a substantial logistical advantage in the field. Deputy Surgeon General has confirmed that Canadian Forces Health Services (CFHS) will seek Health Canada approval of hypertonic saline fluids for military use, in consultation with Defence Research and Development Canada (DRDC) and Department of Defense (DoD).

(U) Le présent projet visait à évaluer l'efficacité, sur le plan de l'amélioration de la survie des patients, de la diminution de la réponse inflammatoire post traumatique et de la réduction du volume de solution nécessaire, de nouvelles solutions hypertoniques de réanimation à administrer en petites quantités en situation de combat. Les résultats indiquent qu'il n'existe aucune différence clinique notable entre l'administration d'une solution saline normale ou hypertonique en ce qui concerne la réanimation des patients en état de choc et des victimes de traumatismes cérébraux. Cependant, du point de vue des soins médicaux militaires opérationnels, le fait de diminuer de 10 % le volume de liquide hypertonique requis (par rapport à la solution saline normale) tout en obtenant les mêmes résultats cliniques confère un avantage logistique important sur le terrain. Le médecin chef adjoint a confirmé que les Services de santé des Forces canadiennes (SSFC) s'adresseront à Santé Canada pour faire homologuer des solutions salines hypertoniques pour utilisation militaire, en consultation avec RDDC et le MDN.

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(U) Combat casualty care; fluid resuscitation; hypertonic saline; resuscitation outcomes consortium; clinical trial; inflammatory response; multiple organ failure; traumatic injury.

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