

Scientific and logistical challenges in designing the CONTROL trial: recombinant factor VIIa in severe trauma patients with refractory bleeding

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Background Clinical research in trauma patients poses multiple challenges in study design. These reflect the heterogeneity of injury and treatment, the paucity of acceptable study endpoints aside from mortality, and the difficulties inherent in obtaining informed consent in acutely ill populations. A current example of this problem is the study of recombinant factor VIIa (rFVIIa), which has attracted considerable interest as a systemic procoagulant agent for use in trauma patients with exsanguinating hemorrhage.

Purpose To report on the implementation of an international trial – CONTROL – intended to assess the efficacy and safety of rFVIIa in trauma, and discuss trauma research study design in light of this experience.

Methods The CONTROL trial international steering committee confronted a number of barriers in the design of the CONTROL trial. They addressed methodologies for (1) standardizing entry criteria for trauma patients suffering inherently heterogeneous injuries, (2) obtaining informed consent in an acutely injured population with altered levels of consciousness, (3) avoiding futile care, while recruiting subjects with incompletely diagnosed injuries, (4) standardizing trauma intensive care across different investigating sites and countries, and (5) establishing study endpoints that were both clinically relevant and convincing to regulatory authorities. The resulting study methodology is reported.

Results The CONTROL trial began active recruitment in October 2005, and was halted on June 11, 2008 because the observed mortality in the 576 enrolled patients was so far below expectations that the study would lack sufficient statistical power at the planned number of subjects to demonstrate a benefit. The utility of the endpoints selected for study will not be known until completion of data analysis.

Limitations Any clinical trial in trauma patients must cope with the urgency of care required, issues of patient heterogeneity, standardization of care across multiple centers, and the difficulties of obtaining informed consent.

Conclusion Research in acutely hemorrhaging trauma patients presents numerous scientific and ethical challenges. The methodology of the CONTROL study is presented as an example of how some of these challenges can be approached and managed, and of the pitfalls that may arise. *Clinical Trials* 2009; 0: 1–13. <http://ctj.sagepub.com>

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Nomenclature

rFVIIa	Recombinant human coagulation factor VII (activated)
US	United States of America
ICU	Intensive care unit
RBC	Red blood cells
CONTROL	The prospective randomized trial of rFVIIa in actively hemorrhaging trauma patients under discussion in this article
FDA	The United States Food and Drug Administration
CFR	Code of Federal Regulations of the United States
DMC	Data monitoring committee
INR	International normalized ratio
MOF	Multiple organ failure
SBP	Systolic blood pressure

Background

Recombinant factor VIIa (rFVIIa) (NovoSeven[®]/Niastase[®], Novo Nordisk A/S, Bagsvaerd, Denmark) is approved for the treatment of hemophilia patients with inhibitors to factor VIII/IX. Since its introduction in Europe in 1996 and the United States in 1999, rFVIIa has attracted considerable interest as a systemic procoagulant agent. There have been numerous case reports and small series describing the successful use of rFVIIa in nonhemophilic bleeding patients with underlying conditions ranging from cirrhosis to hemolytic uremic syndrome to spontaneous intracranial hemorrhage [1–9]. The US Army has reported decreased mortality in the small group of severely injured and massively transfused combat trauma patients who receive early doses of rFVIIa [10]. Phase II prospective, randomized trials have been completed in several populations of interest [11–17]. These have demonstrated generally encouraging therapeutic results without evidence of excess thrombotic risk where used appropriately [11,12,18].

Hemorrhagic shock accounts for 30–40% of all acute deaths from trauma [19–21], and coagulopathic bleeding can contribute greatly to blood loss in trauma [20,22,23]. About 25% of trauma patients are coagulopathic upon arrival in the emergency department [24,25]. Bleeding and transfusion in turn can contribute substantially to mortality and intensive care unit (ICU) morbidity. This is because severely injured patients who survive the initial hemorrhage often go on to develop systemic inflammatory response syndrome, sepsis, and multiple organ system failure [19,21,26–29].

A phase IIb trial of rFVIIa in severely injured trauma patients was performed during the period (2002–2004) and reported in 2005 [11]. In this study, severe injury was defined as physical injuries associated with bleeding that required management with 6 units of red blood cells (RBCs) within 4 h of admission. This trial was powered to demonstrate efficacy of rFVIIa as assessed by the surrogate for bleeding control of reduced transfusion requirements (RBC and other transfusion products used to manage hemorrhage), as well as safety of the dose used. The trial was designed as two parallel studies assessing bleeding control in patients who had experienced blunt trauma and patients with penetrating injuries leading to severe trauma. The trial demonstrated a trend towards reduction in the primary endpoint of RBC transfusion requirement in blunt injury trauma patients who were treated with rFVIIa, after they had required resuscitation for bleeding with at least 8 units of RBCs. This trial also suggested a benefit of treatment with rFVIIa in terms of an impact on late mortality in severely injured trauma patients and a trend towards reduced risk of organ failure, fewer ventilator days, and fewer ICU days. Progression to a phase III trial was strongly indicated. Utilizing the lessons learned from the phase IIb trial, design of this trial: F7Trauma-1711 (the CONTROL study, NCT00184548) began in 2004, and trial enrollment began in 2005.

Issues in trial design

One of the key challenges faced in clinical research is managing variability. Because mechanical trauma is so heterogeneous, a wide variety of factors can affect outcomes. Intrinsic to the problem is that investigators seeking to limit heterogeneity, who choose to focus on populations of very similar patients will limit recruitment into the study. Conversely, investigators including a broad range of patients must accept that intra-group variability may influence outcomes. We identified the following major variables in designing the CONTROL study.

Variability of injury

Traumatic hemorrhage is a heterogeneous event. The application of outside force creates bleeding sites that may be single or multiple, and each anatomic bleeding site bleeds at its own specific rate [21,29,30]. The management of traumatic bleeding crosses traditional surgical specialty lines, creating the need for trauma specialists, who

understand the physiology of bleeding as well as the anatomy of injury. The bleeding sites created by injury differ intrinsically in their potential for harm (i.e., intracranial bleeding is often more critical than injury at extremity sites); in the optimal mode of management (i.e., open operative vs. interventional angiography); in the difficulty inherent in achieving hemostasis (i.e., high-grade liver injury (packing) vs. splenic injuries (splenectomy)); and in their prognosis for survival even in the face of optimal care. Multiple bleeding sites frequently compete for clinical attention, creating second-order effects on outcomes that occur in low numbers, but may have a disproportionate effect on outcomes. Irrespective of bleeding source, coagulopathy is not only seen upon arrival in 25% of the seriously injured, but is often part of the ‘final common pathway’ toward exsanguination and death in these patients [22]. This makes procoagulant therapies like rFVIIa attractive as adjuncts to anatomic source control. But the degree to which the coagulopathic bleeding targeted by rFVIIa accompanies bleeding from primary anatomic sources will vary with the injury itself, as well as depending upon the interventions used to control the primary source. Creating a study that randomizes traumatic bleeding events is challenged at the outset by the inherent variability of the primary injury process.

Variability of patients

Trauma respects no age boundaries, spanning urban penetrating trauma (injuries such as stab or gunshot wounds, common in younger males) where vascular injury leads to severe hemorrhage, to blunt injuries resulting from, for example, motor vehicle crashes (common in young and middle ages, reflecting the greatest proportion who drive), and falls (common in the elderly), in which severe hemorrhage may occur due to a more diffuse injury (compared with penetrating trauma) to internal organs and tissues. Variability in patient age, genetic background, previous state of health, and medical comorbidities can be expected to alter the outcomes of hemorrhage. Older individuals form an increasing subset of fragile trauma victims [31,32]. In these patients, pre-existing comorbidities will markedly increase variance in the outcomes of enrolled patients from an already highly heterogeneous disease.

Variability in prehospital care and transport time

Rural trauma transports entail longer distances and, therefore longer transport times [33], similar

to delays in care that can be observed in military situations. This can create selection bias in several ways. For example, patients with exsanguinating truncal major vascular injuries may not survive to reach medical care in the rural setting. Conversely, long transports may select for injuries that achieve spontaneous hemostasis at low blood pressures. Longer transport times are also associated with the use of larger volumes of crystalloid and, in some locations, colloid resuscitation fluids that may have profound effects upon circulatory physiology. Trauma systems now emphasize rapid transport of bleeding patients to definitive care. Lastly, rural transports may also create special problems with respect to obtaining consent. Nonetheless, many trauma patients are cared for in the rural setting, hence these patient populations must be considered when generalizing treatment effects outside of urban trauma centers. While most mature trauma systems now emphasize rapid transport of bleeding patients to definitive care, the volume of prehospital resuscitation fluids routinely administered has the potential to introduce variability.

Variability in practice

Variability in emergency medical, surgical, and critical care management may introduce substantial differences in patient outcomes from injury. While trauma care has advanced rapidly in the age of evidence-based medicine (e.g., damage control surgery [34,35], tolerance of lower hemoglobins [36–40], lung protective ventilation [41], and glucose control [42]), many controversies still exist and even strong evidence in favor of using specific therapies can be overcome by the persistence of traditional local approaches [43]. Moreover, operative care, especially in patients with multiple injuries, is associated with logistical issues – such as access to surgical suites – that bear on the timing and conduct of operations. Immediate availability of fully staffed operating rooms or rapid access to interventional radiology suites become increasingly important as the rate of bleeding increases, and the preferred approach to anatomic hemorrhage source control may depend upon such local factors.

Variability in consent

International, national, and regional laws for the conduct of emergency research vary widely. In some jurisdictions only the patient or immediate family can provide consent for a research trial [44]. This is of particular relevance in trauma where

almost all seriously injured patients are incapacitated. If the patient is not competent to consent (as is likely) and family cannot be found (also likely) then enrollment becomes impossible [45]. In other areas consent can be obtained from surrogates (i.e., uninvolved physicians or judges who can be briefed about the study in advance). Exception from informed consent requirements for emergency medicine research is legal and easily arranged in some regions, but absolutely prohibited in others. Such factors may diminish the ability to enroll certain types of patients (especially those bleeding most rapidly), thus skewing populations in specific geographic regions toward higher or lower severity.

The need for rapid treatment

Time pressure has a strong influence on recruitment of patients. The 'Golden Hour' concept of trauma care generated in the 1960s emphasized the importance of rapid diagnostic and therapeutic efforts [46]. Current management emphasizes the most rapid possible movement of bleeding trauma patients to definitive care and hemostasis. Thus, successful research in this population requires dedicated personnel, available at all hours of the day and night, and a study design that does not interfere with the normal flow of care.

Variability in acceptable endpoints

Trauma trials often require exception from informed consent (or surrogate mechanisms), if patients are to be enrolled soon after injury. The United States Food and Drug Administration (FDA) has authorized these trials requiring exception from informed consent in the past, but has required that they use mortality as the primary scientific endpoint since patients must be in a life-threatening situation [47]. Although mortality as an endpoint is not a requirement of CFR 21 50.24, this FDA practice has strongly influenced study designs in trauma over the past decade, particularly because the factors elucidated above require a large number of enrolled patients to demonstrate a change in mortality. Moreover, more than 90% of admitted trauma patients are at very little risk of dying, while an additional 3–5% are so severely injured that no therapy will be effective. This leaves a small selected faction ($\approx 5\%$) who could potentially qualify for an acute trauma intervention study [48]. Investigators must, therefore, choose between enrollment criteria tightly focused on the population of interest – accepting that recruitment

will be infrequent – or broaden the enrollment criteria and plan to enroll more patients. This question of 'signal versus noise' is a key challenge in trauma study design. Combination of the community consultation process with a mortality endpoint means that the normal phase I, II, and progression of data and experience is circumvented, and institutions and companies are required to proceed directly from preclinical data to definitive phase III trials.

All of these issues were considered in the design of the CONTROL trial, and examined at length. We offer this description of the resulting methodology in the hope that lessons learned may benefit other researchers.

Roles and responsibilities

CONTROL was funded by Novo Nordisk A/S, the manufacturers of rFVIIa. Novo Nordisk A/S and the CONTROL investigators provided education for the research monitors in the assessment of trauma patients, in the normal flow of trauma care, and in the likely and unlikely complications that can result.

The CONTROL Steering Committee is composed of surgeons, intensivists, anesthesiologists, and study design experts with experience in trauma research (Appendix A).

The role of the Steering Committee is to provide expert advice on all aspects of the protocol including original construct, amendments, statistical analysis planning, and presentation of results. The Steering Committee serves as the author group for the anticipated manuscripts that will report the findings of the study. Independent of the Steering Committee, Novo Nordisk A/S has chartered a Data Monitoring Committee (DMC) for the overview of safety in the CONTROL study (Appendix B). The DMC was established according to international guidelines [49–54].

The enrollment milestones at which data must be reviewed for safety surveillance were defined prior to study initiation. All DMC functions, including statistical analysis, are conducted independently of the Steering Committee and unblinded reviews are conducted independently of the sponsor.

In order to decrease protocol deviations and assure compliance with enrollment guidelines, the Vanderbilt Coordinating Center, Vanderbilt University, Nashville, TN – an academic research organization – was engaged by Novo Nordisk A/S to provide an ongoing medical quality assurance review. It was recognized that many facets of the enrollment process would be key to the ultimate success of the trial. Thus, it was expected that

without vigorous oversight potential, patients who were marginal or inappropriate for the study might be enrolled, thus decreasing the desired ‘signal to noise’ ratio. The coordinating center’s review focused on appropriateness of enrollment and adherence to practice guidelines (damage control surgery, transfusion therapy, and ventilator management). Findings of their review were provided to hospitals, investigators, and the Steering Committee within weeks of a patient’s enrollment, as part of a continuous quality improvement process. The coordinating center was also available for questions arising from the conduct of the study at each site.

Basis for study design

Development of the study protocol was preceded by analysis of published and unpublished data from the prior phase IIb trial of rFVIIa in trauma patients [11], and by examination of retrospective data obtained from the Traumaregister of the German Society for Trauma Surgery, the United States’ National Trauma Data Bank, and the trauma registries of the University of Memphis, the New Jersey State Trauma Center at Newark, and the R Adams Cowley Shock Trauma Center of the University of Maryland. Our goal was to establish the observed mortality and incidence of major organ system failure in patients presenting with bleeding refractory to standard treatment. We were interested in the correlation between these outcomes and diagnostic data available to clinicians in the first few minutes of care. Our intention was to identify enrollment criteria that would meet the following four priorities: (1) inclusion of patients with bleeding that was substantial and predictive of poor outcomes and not able to be controlled, (2) elimination of patients with controlled or low-rate hemorrhage (likely to survive regardless of treatment), (3) elimination of moribund patients already in a terminal state of shock (unlikely to survive with any therapy), and (4) inclusion of a sufficient number of patients at each contributing center so as to develop ‘research expertise’ in these locales.

Diagnostic data included trauma mechanism, initial blood pressure, specific injuries, Glasgow Coma Scale score, and laboratory data (hemoglobin concentration, prothrombin time/international normalized ratio (INR), lactate, base deficit (decrease in serum bicarbonate often indicating metabolic acidosis), and pH). Outcome data included: the incidence and timing of mortality, ventilator-free days (days alive and free of pulmonary dysfunction requiring on-going medical intervention through day 30), intensive care-free

Table 1 Impact of head injury and base deficit on mortality, based on patient data from the Traumaregister of the German Society for Trauma Surgery. Profile of patients included in the analysis: Injury Severity Score >16; age 18–65 years; primary admission; blood pressure <90 or BE ≥5 or volume loading at admission >2000 mL; red blood cells >6 units; no cardiopulmonary resuscitation or SBP ≤50, or sole extremity injuries

	Mortality (%)	
	Base deficit worse than 15 mEq/L	Base deficit worse than 20 mEq/L
Brain AIS=0	12.4	12.8
Brain AIS=1+2	11.8	12.3
Brain AIS=3	15.7	16.6
Brain AIS=4	34.8	35.9
Brain AIS=5+6	57.1	59.0

AIS, Abbreviated Injury Score.

Data presented with permission from Rolf Lefering on behalf of the Traumaregister of the German Society for Trauma Surgery.

days (days alive and free of need for ICU care through day 30), need for renal replacement therapy (days alive and free of renal dysfunction requiring on-going medical intervention through day 30), and total transfusion requirements (Table 2).

As an example, Table 1 shows the impact of head injury (abbreviated injury scale) and of base deficit on mortality, based on data from the Traumaregister of the German Society for Trauma Surgery, and is presented as one example of our analysis. Similar graphics were generated for other variables and correlations. These were considered by the CONTROL Steering Committee in selecting study inclusion and exclusion criteria that would best meet the stated priorities.

Study design

CONTROL was a multicenter, prospective, randomized, parallel-group, double-blind placebo-controlled study of rFVIIa in the early treatment of trauma patients with life-threatening hemorrhagic shock.

The primary objective of CONTROL was to assess the effect of rFVIIa on 30 day mortality and durable morbidity in patients with severe traumatic injury (blunt and/or penetrating injuries). Secondary outcomes included RBCs, total transfusions (30 day), multiple organ failure (MOF)-free or ICU-free days (out of 30) and safety (over 90 days).

CONTROL was an international trial, including more than 100 high-volume trauma centers on six continents. Under the protocol, rFVIIa or placebo were given early in the resuscitation of severely

injured patients with ongoing hemorrhage. Drawing on lessons learned from other researchers, many aspects of clinical care that might have impacted on study endpoints were standardized in the study protocol.

Inclusion and exclusion criteria

CONTROL inclusion and exclusion criteria identified patients with trauma injury (blunt and/or penetrating) with evidence of active hemorrhage (torso and/or proximal lower extremity), refractory to standard treatment.

Specifically, blunt and/or penetrating trauma patients 18–70 years old were eligible if they had continuing torso and/or proximal lower extremity bleeding after receiving 4 units of RBCs despite standard hemostatic interventions. Acceptable markers of active bleeding were continuing hypotension (systolic blood pressure (SBP) ≤ 90 mm Hg), acidosis (lactate > 6 mmol/L or base deficit ≥ 5 mEq/L), or intravenous fluid requirements of ≥ 1 L/h to maintain vital signs before randomization. Patients who were moribund, had severe brain injuries, or were injured > 12 h before randomization or > 4 h before hospital arrival were excluded.

Our intent was to focus study enrollment on those patients in hemorrhagic shock most likely to benefit from rFVIIa therapy. The Steering Committee decided to make study intervention take place earlier than at the 8 units of RBCs used as the entry criterion in the phase IIb trial. The need for 8 units of RBCs in the management of a patient with severe hemorrhage would normally indicate a patient already in, or close to, hemorrhagic shock and very rapidly exsanguinating. The decision to initiate therapy with the study agent rFVIIa before this point was reached was based on our hypothesis (based on clinical suspicion) that rFVIIa would have greater benefit when used early in resuscitation, prior to the development of significant hypothermia and acidosis, or the dilution of autologous coagulation factors. At the same time, stringent criteria were added to ensure that patients were still *actively* bleeding at the time of enrollment. This was aimed at reducing the ‘noise’ of patient enrollments in which conventional therapy would likely be or already had been successful. These important changes to the entry criteria were intended to encourage earlier entry into this study than was achieved in the previous phase IIb trauma study. But while physiologically appealing, this approach was expected to exacerbate consent problems in countries requiring individual or family consent as opposed to emergency consent.

With respect to strengthening exclusion criteria, a major emphasis was placed on the elimination of moribund patients from the CONTROL trial. It was felt that this group had weakened the ability to detect drug effect in the phase IIb trial. In crafting this exclusion, the Steering Committee relied on the trauma registries listed above as well as published and unpublished case series of rFVIIa use in trauma [55], and the clinical expertise of the members.

Consent for enrollment in CONTROL was the same in all countries: informed consent was obtained prospectively from the patient (the capacity to give consent for those truly eligible for inclusion given the nature of injuries and interventions can be debated) or a legally authorized representative. In some countries a representative can be an independent physician, lawyer, or administrator designated to represent the patient’s interests. In these cases study investigators briefed this individual about the CONTROL trial in advance, allowing time for a fully informed and interactive discussion. In the United States and a few other participating countries (Brazil, Finland, and Turkey), legal representatives are defined by individual state law and local hospital policy, and are usually limited to family members or predesignated guardians. This circumstance thus requires a full informed consent discussion at the time of patient admission to the trauma center, when the patient has become eligible for the study and the family has been located. Based on experience from similar trials, the Steering Committee estimated that this would reduce achieved enrollment in US centers by 50–90% [45]. Consequently, we discussed the need to seek exceptions from informed consent under the provisions of US Code 21CFR50. Our decision to proceed without the exceptions from informed consent was made with the desire to begin enrollment worldwide as soon as possible, and with the understanding that data on the eligible cohort as well as those actually enrolled would be gathered from all centers.

In other countries similar local law has been challenged. In Sweden, a letter from the involved study sites to the Swedish Health Authorities argued for the need of a different consent procedure. The trial was given permission to deviate from the law to define the representative as an independent physician. It is not clear if these differing standards for acceptable consent introduced differences in the cohorts by country of origin or not, but this question will be an important point of analysis. It is possible that a greater proportion of slower bleeding patients (e.g., pelvic fracture as opposed to penetrating vascular injuries) were included in countries requiring consent from the patient’s family. It is also likely that rapidly

exsanguinating patients were unable to be enrolled if they were in a country requiring next-of-kin or similar consent due to time constraints. Support for this hypothesis comes from two recent publications relating to rapidly exsanguinating patients. Moore *et al.* [56] showed that the majority of massively transfused trauma patients reach the point of requiring 6–10 units of RBC within 3–4 h of admission and that the majority who die do so within 3–4 h. Dutton *et al.* [45] documented that consent was possible in <50% of all seriously injured trauma patients within 3–4 h of admission. Taken together, the majority of the exact population of interest, i.e., rapidly bleeding and massively transfused patients, die before consent can be obtained.

Study flow

Figure 1 shows the study protocol for an individual patient. Investigational drug dosing occurred as soon as possible after the fourth unit of RBC transfusion, and absolutely before the eighth unit. The dose of rFVIIa used was identical to the phase IIb trial: 200 µg/kg initially, followed by 100 µg/kg 1 h later and 100 µg/kg 2 h after that [11,57]. The Steering Committee debated use of a lower dose of active agent, as described in numerous case reports and series in trauma patients [7,58,59], but chose to keep CONTROL consistent with the positive phase IIb trial. This dose was originally based on the recommended plasma level of 50 nM of rFVIIa needed for effective coagulation in hemophilia patients [57] and the pharmacokinetics of rFVIIa in trauma found in the prior phase IIb trial [11]. It was felt that the benefits of maintaining this plasma level through the first 6–8 h of care would outweigh the potential risks of repeated

dosing of FVIIa in a patient who had stopped hemorrhaging.

Statistical considerations

Total enrollment for the CONTROL trial was determined by the sponsor, in collaboration with the Steering Committee, pursuing a power of 80% to demonstrate significance on the primary endpoint (with a type I error of 2.5%). The primary endpoint involved testing of the mortality difference, followed potentially by testing of the morbidity difference. If initially a superiority mortality difference could not be demonstrated, the morbidity difference was tested, provided that the mortality difference was at least noninferior. The sample size assumptions borrowed from the preceding phase IIb trial, reported mortality rates of ~25% and 30% for rFVIIa and placebo, respectively, and morbidity rates of 5% and 10%.

Sample-size calculations were based on comparisons of mortality for the intent-to-treat population using the one-sided chi-square test (significance level 2.5%). The goal was to detect a 16.7% mortality reduction with rFVIIa, assuming 30% mortality in placebo patients. This estimate was based on the prior phase IIb trial [11] and reviews of three trauma registries (M. Croce, University of Tennessee Health Science Center, Memphis, TN, USA; R. Levering, German Trauma Registry, University of Witten/Herdecke Cologne, Germany; R. Lavery, UMDNJ-New Jersey Medical School, NJ, USA, personal communications). The probability of demonstrating efficacy of the primary endpoint was estimated at 80.1% for a sample size of 1276 blunt trauma patients.

Further secondary endpoints for analysis (e.g., transfusion requirement) were prospectively

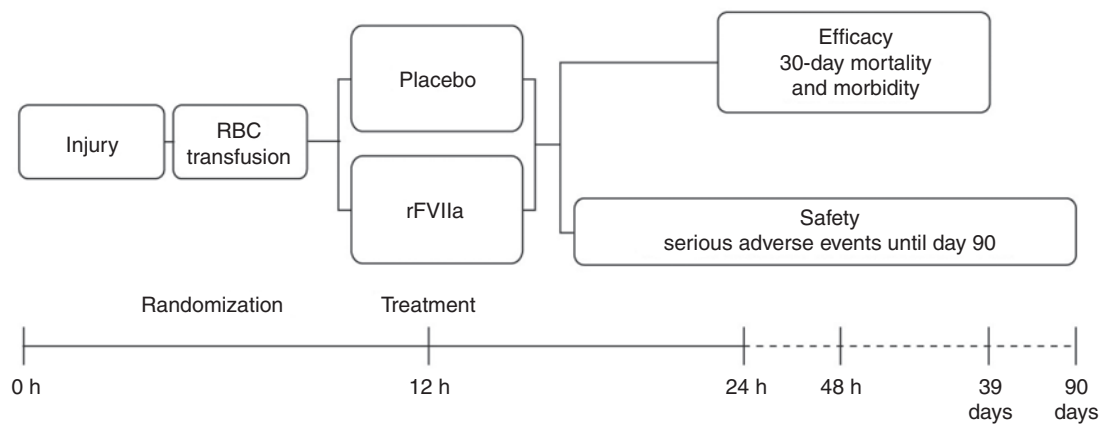


Figure 1 Flowchart for the CONTROL protocol RBC

Table 2 CONTROL secondary endpoints

Endpoint	Time frame	Designated as a safety issue
Days alive and free of pulmonary and/or renal dysfunction requiring ongoing medical intervention	Through day 30	No
Time to death from time of first dose	Through day 30	No
Number of transfused RBCs from time of first dose	Through hour 24	No
Number of patients receiving 10 units or more of RBCs from time of injury	Through hour 24	No
Total number of allogeneic transfusions from time of first dose	Through hour 24	No

Table 3 Additional end points of CONTROL. The effect of recombinant factor VIIa vs placebo on the following variables will also be analyzed

Clinical variable	Analysis
Safety looking at arterial thrombotic events	By risk factors
Use of FFP and platelets, ratio	Outcome mortality and morbidity
Coagulopathy and physiologic state	By degree hypothermia, acidosis, and early coagulopathy
Ventilator-free days	By adherence to guidelines
Source of bleeding	By looking only at days on the ventilator related to trauma
Trauma care outcome	Risk/benefit – outcome
	Prehospital interventions
	Fluid management variations and outcomes
	Impact of time/delay to definitive care (and time to ICU)
	Impact of the trial guidelines, compliance, and outcomes
	Country or region variations in outcome
	Given the complexity of the trial and significant learning curve, with removal of the first patient in each site and repeat all the analyses
Baseline ALI/ARDS analyzed by treatment arm	Rate of ventilator-free days per treatment arm

ALI/ARDS, acute lung injury/acute respiratory distress syndrome; FFP, fresh frozen plasma; ICU, intensive care unit.

defined and prioritized by the Steering Committee based on their potential utility to clinicians and their potential to support the primary endpoint (Table 2). In addition to the predefined analyses of the primary and secondary endpoints, the Steering Committee prospectively proposed to the Sponsor an analysis of the effects of rFVIIa on a number of additional clinical variables, as listed in Table 3. Outcomes would be assessed separately in blunt and penetrating trauma patients, with the blunt trauma group (expected to be substantially larger) being the primary group for assessing efficacy.

An interim analysis for futility by the DMC was planned after inclusion of one-third of the planned number of blunt trauma patients.

Treatment guidelines

The conceptual basis of surgical management of hemorrhage in critically injured patients is the 'Damage Control' principle [30,34]. This approach emphasizes timely diagnostic studies focused on

finding and treating bleeding, rapid interventions to control primary hemorrhage sources, and deferral of all nonessential procedures (e.g., orthopedic fixation) that can cause an aggregate increase in bleeding for at least 24 h following complete resuscitation. The participating sites in the CONTROL trial were selected on the basis of their ability to meet this standard. All sites have a dedicated trauma care team, immediate surgeon/operating room availability, a well-organized critical care environment, and established performance improvement policies.

The study protocol included guidelines for fluid resuscitation and transfusion. Unstable patients were managed empirically at the discretion of the attending physician, but in more stable patients transfusion was based upon diagnostic data. In general, fluid administration was continued until serial assays confirmed the resolution of shock (lactate and base deficit within normal limits). In actively bleeding patients, transfusion of RBCs was targeted to a hemoglobin concentration of 8–10 g/dL. Transfusion of fresh frozen plasma was

targeted to an INR < 1.5, transfusion of cryoprecipitate/fibrinogen to a minimum of 100 mg/dL, and transfusion of platelets to a minimum of 50,000 per mm³. In hemodynamically stable patients, RBC 'transfusion triggers' were lowered to 7 g/dL [60,61], and clotting factors and platelets were only indicated in the presence of active bleeding or in anticipation of surgical blood loss. Because of their effects upon hemostasis, starch solutions were limited to a total volume of 2000 mL per 24 h and dextran solutions were prohibited.

The Steering Committee also defined a protocol for ventilator management. The protocol emphasized the 'lung-protective' strategies established in clinical trials by the ARDSnet research group [62], consisting of low to moderate tidal volumes and limited inspiratory pressure. Spontaneous breathing trials were timed with daily interruptions of sedation. In stable patients, daily weaning trials were mandated with a defined pathway to liberation from positive-pressure ventilation at the earliest possible moment. The actual timing of extubation was allowed to depend on clinical logistics such as upcoming surgical procedures and the need for airway protection. Assessment of the 'ventilator-free days' endpoint will depend only upon the patient's ability to oxygenate and ventilate without mechanical support (and not on the removal of the endotracheal tube).

Compliance with Guidelines

Practice variation and related variability in clinical outcome contributes substantial 'noise' to clinical research. In an attempt to minimize inappropriate practice variation in the care of trauma patients, evidence-based treatment guidelines were established and promulgated. Adherence to these guidelines was actively monitored by the Vanderbilt Coordinating Center. These standards were defined in the protocol, explained during the site survey and recruitment phases, and reinforced at ongoing investigator meetings. Individual, center-specific feedback provided by the coordinating center following each enrollment further emphasized the focus on evidence-based care. Guidelines were loosely drawn to allow individualization of patient care. Care remained the responsibility of the patient's attending physicians, but the CONTROL guidelines outlined a 'best practice' and provided templates for when deviations should be documented, justified, or reviewed.

Use of ongoing and immediate high-level medical review is novel in trauma trials, but was appropriate given the complexity of CONTROL and its international reach. The Vanderbilt Coordinating Center is an organization made up

of nurses and physicians with significant experience in both trauma care and multicenter research projects in the critical care arena. Following thorough familiarization with the CONTROL protocol, the ongoing task of the center was to review immediate clinical data on each new enrollment (a 'short form' including data up to Day 5, required of each center within 10 days of enrollment) and provide rapid feedback to the center on data completeness and quality as well as on adherence to inclusion/exclusion criteria, protocolized study procedures, and protocolized supportive care as described in the treatment guidelines below. Protocol deviations or inappropriate enrollments were identified and discussed with the on-site investigators. Repeated or systematic deviations were referred to the Steering Committee and to the sponsor for review and more serious remediation, which could include discontinuation of a study site. This dialogue was intended to be interactive, with the coordinating center serving as a resource to individual site investigators with questions or concerns.

Study progress

Site selection for CONTROL began in mid-2005. Potential sites were nominated by Steering Committee members or Novo Nordisk A/S representatives and contacted regarding their interest. Initial screening by way of a questionnaire to establish patient volumes and broad policies was followed by a site visit conducted by a Novo Nordisk A/S physician and clinical operations staff. A series of meetings designed to educate investigators, study coordinators, nurses, and pharmacists were held in late 2005. The initiation of the first sites occurred in late summer of 2005. The first patient was enrolled in CONTROL in October 2005, in Austria.

Issues encountered during the study

Following initial site selection and initiation, many sites were closed either due to lack of eligible patients or study staff resources. At its conclusion, there were 75 active sites participating in CONTROL in 24 countries, including 10 centers in the United States. All in all 151 investigational sites were initiated; of those that were closed during the conduct of the trial, most were due to none or very low enrollment.

As the criteria for enrollment were quite stringent, a limited number of patients were eligible at each site, lowering the average enrollment.

This required constant focus on trial education. Site personnel typically change on a regular basis and therefore continuous training was required. The sponsor had designated recruitment managers and training managers to visit sites on a frequent basis in order to keep a constant high level of education and focus at the sites. Ongoing scientific monitoring by the Vanderbilt Coordinating Center corrected and clarified numerous small inconsistencies between centers, but revealed no systematic issues with patient enrollment or management. Enrollment and exclusion criteria were generally well adhered to, and there were no substantial differences in protocol violations between countries or regions.

Prior to examining the question of statistical power, the DMC conducted its preplanned review of the first 450 patients enrolled and found no significant safety issues. As of March 1, 2008 American trauma centers had enrolled ~14% of eligible patients, based on the requirements for informed consent outlined above.

An interim analysis for futility was reached in March 2008, and the decision to stop the trial was announced in June. Statistical analysis (by the DMC only; the Steering Committee has not reviewed any outcome data) had revealed that the mortality observed in all enrolled patients was lower than expected during study design, meaning that the study as a whole would be underpowered to assess the primary endpoint. Several thousand patients, representing up to a decade of recruitment, would be required to generate sufficient statistical power. The sponsor chose to close the study, with a total enrollment of 576 patients. Unblinding of the data, analysis, presentation, and publication will occur over the coming year.

Conclusion

Significant discussion has ensued in recent years concerning the ethics of emergency research. Many strongly held opinions have been voiced, in multiple forums. Many of these opinions appear contradictory, yet most researchers – including the Steering Committee – agree that emergency research is ethically justifiable and must be done if outcomes from trauma are to improve.

The design and implementation of the CONTROL trial illustrates the broad set of issues facing researchers in trauma and acute-care medicine. Difficulty still exists in the definition of early enrollment criteria, i.e., early in the course of serious bleeding. These could be enhanced by prediction algorithms based on data available within the first minutes after arrival in an

emergency department. As is illustrated here, the most difficult problem for researchers is designing a trial that has a mortality endpoint in an era when trauma mortality is already very low and stable. The use of mortality endpoints necessitates enrollment of large numbers of patients and may render some studies impracticable due to excessive study duration or enormous expense. Other endpoints that can be tested on smaller numbers of patients must be sought. These should permit conclusive studies to be conducted on manageable numbers of patients. The current practice of legally authorized representatives or exception from consent in the US and the role US investigators and patients can play in global studies, where exception from consent is not required need to be better clarified. A process allowing the performance of phase I and II emergency research also needs to be developed. Ultimately a process where phase I, II, and III studies of interventional trauma trials, within minutes of admission, must be agreed upon. Not doing so will likely lead to delayed improvement in trauma outcomes.

While the benefit of rFVIIa in trauma will not be known until the study analysis is concluded – and perhaps not even then – the lessons learned from designing and conducting the study may be of use to future investigators and their sponsors.

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