

Relevant Academic Literature, Applicable Federal  
Regulations for the Protection of Human Subjects

on

Emergency Research Involving Artificial/Substitute  
Blood Products  
(including PolyHeme®)

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## Federal Regulations for the Protection of Human Subjects and the Emergency Waiver of Informed Consent

### Background

Federal oversight of research involving human subjects is found in two regulatory regimes within the Department of Health and Human Services (DHHS),

- Food and Drug Administration (FDA).
  - 21 CFR 50, 56  
[<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm)
- the Office of Human Research Protections (OHRP), and
  - 45 CFR 46  
[<http://www.hhs.gov/ohrp/humasubjects/guidance/45cfr46.htm>](http://www.hhs.gov/ohrp/humasubjects/guidance/45cfr46.htm)

Generally, any research that is testing a drug, device, or other product that will be submitted for FDA approval must follow their regulations (21 CFR 50/56), while research that is supported by federal funds (e.g., an NIH grant) must also comply at a minimum with 45 CFR 46 Subpart A (the federal policy for the protection of human subjects, also known as *the Common Rule*), and with Subparts B,C,D as appropriate.

While most of the FDA and OHRP regulations are similar (or substantially overlap), there are a number of areas in which they differ.

Further, all institutions supported by federal funds must negotiate a Federalwide Assurance with OHRP that provides for all research within an institution to be subject to the Common Rule, regardless of whether the research is federally funded.

### History of Emergency Waiver of Informed Consent

**June 18, 1991:** the basic DHHS policy (Common Rule) for protection of human subjects outlines the authority of the department or agency head to waive the applicability toward any particular research activity of any part of the human subjects protection policy. See 45 CFR 46.101(i).

“(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes or research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, and shall also

publish them in the FEDERAL REGISTER or in such other manner as provided in Department or Agency procedures.<sup>1</sup>

**November 1, 1996:** the DHHS used their authority to waive the applicability of the Common Rule requirement for informed consent in cases of emergency medical research that are subject to FDA regulation.

“The Food and Drug Administration (FDA) is amending its current informed consent regulations to permit harmonization of the Department of Health and Human Services’ (DHHS) policies on emergency research and to reduce confusion on when such research can proceed without obtaining an individual subject’s informed consent. This regulation provides a narrow exception to the requirement for obtaining and documenting informed consent from each human subject, or his or her legally authorized representative, prior to initiation of an experimental intervention. The exception would apply to a limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition, and who do not have a legally authorized person to represent them. FDA is taking this action in response to growing concerns that current rules are making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized.” See Federal Register 51498

Effectively, this waiver means that if an emergency research study meets the FDA criteria for the exception from standard informed consent in 21 CFR 50.24, the OHRP will waive the Common Rule requirements for informed consent. (See FR page 51531)

Any IRB is allowed to approve emergency research not containing standard consent procedures, so long as that research meets the FDA criteria in 50.24 for exception from informed consent. Briefly, these criteria involve

“A limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition, and who do not have a legally authorized person to represent them.”

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<sup>1</sup> <sup>1</sup> Institutions with HHS-approved assurances on file will abide by provisions of Title 45 CFR part 46 subparts A-D. Some of the other departments and agencies have incorporated all provisions of Title 45 CFR Part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, subpart C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.”

- ❖ Read the Information Sheet on the “Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble.”  
<<http://www.fda.gov/oc/ohrt/irbs/except.html>>
- ❖ Read the entire “Draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors on the Exception from Informed Consent Requirements for Emergency Research”  
<[http://www.fda.gov/ora/compliance\\_ref/bimo/err\\_guide.htm](http://www.fda.gov/ora/compliance_ref/bimo/err_guide.htm)>

### **Selected Academic Literature**

The following represents three categories of the relevant literature on artificial blood substitutes and emergency research from 1999 to the present. Where available, the abstracts have been listed.

- 1) The Science of Blood Substitute Research  
This literature covers the biochemical research involving blood substitutes including molecular analyses of polymerized hemoglobin. There involve study reports of the efficacy and use of diaspirin cross-linked hemoglobin, as well as pharmacological discussions of blood substitute side effects and mortality analyses. Finally, several review articles are present, including discussions on the present and future application of blood substitutes.
- 2) The Ethics and Law of Emergency Research in General  
These articles cover many of the considerations involved in use of the consent waiver: a brief history of the development of the consent waiver, how much effort should be made to obtain actual consent, the extent of the duty to notify the community that there is active use of such waivers, the impact of waiver use on research participation and public perception of research, how IRBs should handle studies involving emergency and resuscitative research, and actual patient responses to the idea of being subjected unknowingly to similar research.
- 3) The Ethics and Law of Emergency Research Involving Blood Substitutes  
This literature looks at how the emergency waiver has been applied in cases where blood substitutes are administered in trauma settings. The appropriateness of the application of the consent waiver is discussed, as well as the process and timeline by which consent is obtained after treatment.

## **1. The Science of Blood Substitute Research**

Cheung AT, Duong PL, Driessen B, Chen PC, Jahr JS, Gunther RA. **Systemic function, oxygenation and microvascular correlation during treatment of hemorrhagic shock with blood substitutes.** *Clinical Hemorheology and Microcirculation*. 2006;34(1-2):325-34.

Systemic function and oxygenation changes during hemorrhagic shock treatment were continuously monitored and correlated with real-time microvascular changes. After splenectomy, each dog (n=12) was hemorrhaged (MAP= approximately 50 mmHg; approximately 40% blood loss=32-36 ml/kg) and randomly assigned to 4 resuscitation groups: autologous/shed blood, hemoglobin-based oxygen-carrier/Oxyglobin((R)), crystalloid/saline, and colloid/Hespan((R)). Systemic function and oxygenation changes were continuously monitored and measured using standard operating room protocols. Computer-assisted intravital microscopy was used to non-invasively videotape and objectively analyze and quantify real-time microvascular changes in the conjunctival microcirculation. All measurements were made during pre-hemorrhagic (baseline), post-hemorrhagic and post-resuscitation phases of the study. Pre-hemorrhagic microvascular changes were similar in all 12 dogs (venular diameter=43+/-12  $\mu$ m; red-cell velocity=0.6+/-0.2 mm/s). All dogs showed similar significant ( $P<0.01$ ) post-hemorrhagic microvascular changes: approximately 20% decrease in venular diameter; approximately 80% increase in red-cell velocity. These microvascular changes correlated with post-hemorrhagic systemic function and oxygenation changes. The resuscitations restored microvascular changes to pre-hemorrhagic values; the microvascular reversals also correlated with post-resuscitation systemic function changes in all groups. However, only shed blood resuscitation restored oxygenation level close to pre-hemorrhagic values. All 12 dogs survived resuscitation treatments despite differences in oxygen-carrying capability between groups.

Yu B, Liu Z, Chang TM. **Polyhemoglobin with different percentage of tetrameric hemoglobin and effects on vasoactivity and electrocardiogram.**

*Artificial Cells, Blood Substitutes, and Immobilization Biotechnology*. 2006;34(2):159-73.

There has been considerable discussions on why some types of haemoglobin-based blood substitutes increase vasoactivity whereas a very few others do not. In this study, we prepare four different types of PolyHb each containing different percentage of tetrameric hemoglobin using glutaraldehyde crosslinking and characterized to ensure that they all have the same oxygen affinity. Thus the preparations are prepared from the same chemical method and have the same oxygen affinity. We infused these in the form of 1/6 volume toploading into anesthetized rats to simulate the use of blood substitutes in surgery. Mean arterial pressure (MAP) increased immediately after injection of PolyHb containing 38% or 78% of tetrameric hemoglobin. However, there was no significant increase in blood pressure with the injection of PolyHb containing 16% or 0.4% tetrameric hemoglobin. In electrocardiogram (ECG) study, we observe that high percentage (78%) of tetrameric hemoglobin causes marked changes in ECG immediately after infusion. Injection of PolyHb containing 16% or 38% of tetrameric hemoglobin resulted in minimal elevation of the ST segment. Infusion of PolyHb containing 0.4% of tetrameric hemoglobin did not result in any changes.

Spahn DR, Kocian R. **Artificial O<sub>2</sub> carriers: status in 2005.**

*Current Pharmaceutical Design*. 2005;11(31):4099-114. Review.

Donor blood is a limited resource and its transfusion is associated with significant adverse effects. Therefore, alternatives have been searched, the ultimate being artificial oxygen (O<sub>2</sub>) carriers. There are two main groups of artificial O<sub>2</sub> carriers: hemoglobin based and perfluorocarbon emulsions. The hemoglobin molecule in hemoglobin based artificial O<sub>2</sub> carriers needs to be stabilized to prevent dissociation of the  $\alpha_2\beta_2$ -hemoglobin tetramer into  $\alpha\beta$ -dimers in order to prolong intravascular retention and to

eliminate nephrotoxicity. Other modifications serve to decrease O<sub>2</sub> affinity in order to improve O<sub>2</sub> off-loading to tissues. In addition, polyethylene glycol may be surface conjugated to increase molecular size. Finally, certain products are polymerized to increase the hemoglobin concentration at physiologic colloid oncotic pressure. Perfluorocarbons are carbon-fluorine compounds characterized by a high gas dissolving capacity for O<sub>2</sub> and CO<sub>2</sub> and chemical and biologic inertness. Perfluorocarbons are not miscible with water and therefore need to be brought into emulsion for intravenous application. Development, product specification, physiologic effects, efficacy to decrease the need for donor blood in surgery and side effects of the following products are described: Diaspirin cross-linked hemoglobin (HemAssist), human recombinant hemoglobin (rHb1.1 and rHb2.0), polymerized bovine hemoglobin-based O<sub>2</sub> carrier (HBOC-201), human polymerized hemoglobin (PolyHeme), hemoglobin raffimer (Hemolink), maleimide-activated polyethylene glycol-modified hemoglobin (MP4) and perflubron emulsion (Oxygent). In addition, enzyme cross-linked poly-hemoglobin, hemoglobin containing vesicles (nano-dimension artificial red blood cells) and an allosteric modifier (RSR13) are discussed. The most advanced products are in clinical phase III trials but no product has achieved market approval yet in the US, Europe or Canada.

Moore EE, Johnson JL, Cheng AM, Masuno T, Banerjee A **Insights from studies of blood substitutes in trauma.** *Shock*. 2005 Sep;24(3):197-205. Review.

Most authorities believe that the greatest need for blood substitutes is in patients with unanticipated acute blood loss, and trauma is the most likely scenario. The blood substitutes reaching advanced clinical trials today are red blood cell (RBC) substitutes, derived from hemoglobin. The hemoglobin-based oxygen carriers (HBOCs) tested currently in FDA Phase III clinical trials are polymerized hemoglobin solutions. The standard approach to restoring oxygen delivery in hemorrhagic shock has been crystalloid administration to expand intravascular volume, followed by stored RBCs for critical anemia. However, allogenic RBCs may have adverse immunoinflammatory effects that increase the risk of postinjury multiple organ failure (MOF). Phase II clinical trials, as well as in vitro and in vivo work, suggest that resuscitation with a HBOC--in lieu of stored RBCs--attenuates the systemic inflammatory response invoked in the pathogenesis of MOF. Specifically, an HBOC has been shown to obviate stored RBC provoked neutrophil priming, endothelial activation, and systemic release of interleukins 6, 8, and 10. Based on this background and work by others, we have initiated a multicenter prehospital trial in which severely injured patients with major blood loss (systemic blood pressure <90 mmHg) are randomized to initial field resuscitation with crystalloid versus HBOC. During the hospital phase, the control group is further resuscitated with stored RBCs, whereas the study group receives HBOC (up to 6 units) in the first 12 h. The primary study endpoint is 30-day mortality, and secondary endpoints include reduction in allogenic RBCs, hemoglobin levels <5 g/dL, uncrossmatched RBCs, and MOF. The potential efficacy of HBOCs extends beyond the temporary replacement for stored RBCs. Hemoglobin solutions might ultimately prove superior in delivering oxygen to ischemic or injured tissue. The current generation of HBOCs can be lifesaving for acute blood loss today, but the next generation might be biochemically tailored for specific clinical indications.

Thyes C, Spahn DR. **Current status of artificial O<sub>2</sub> carriers.** *Anesthesiology Clinics of North America*. 2005 Jun;23(2):373-89, viii. Review.

This article describes currently evaluated artificial O<sub>2</sub> carriers, summarizes their efficacy, and discusses their side effects, based on and restricted to published data. For compounds in phase III testing, approximately 500 to 1000 patients have been dosed, and similar numbers of control patients have been investigated. For compounds in phase I or II testing, the number of patients dosed is significantly less. Unfortunately, there is a significant amount of unpublished data, which renders the overall assessment difficult, and the direct comparison among different types of artificial O<sub>2</sub> carriers is significantly limited by the virtual nonexistence of studies that directly compare different products.

Bone HG, Westphal M. 2005. **The prospect of hemoglobin-based blood substitutes: Still a long stony road to go.** *Critical Care Medicine*. 2005 Mar;33(3):694-5.

**Sloan, EP. The clinical trials of diaspirin cross-linked hemoglobin (DCLHb) in severe traumatic hemorrhagic shock: the tale of two continents.**

*Intensive Care Medicine.* 2003 Mar;29(3):347-9.

**Moore EE. Blood substitutes: the future is now.**

*Journal of the American College of Surgery.* 2003 Jan;196(1):1-17.

**DCLHb Traumatic Hemorrhagic Shock Study Group. Post hoc mortality analysis of the efficacy trial of diaspirin cross-linked hemoglobin in the treatment of severe traumatic hemorrhagic shock. *Journal of Trauma.* 2002 May;52(5):887-95.**

The efficacy trial of diaspirin cross-linked hemoglobin (DCLHb) in traumatic hemorrhagic shock demonstrated an unexpected mortality imbalance, prompting a three-step review to better understand the cause of this finding. **METHODS:** Patients were enrolled in this DCLHb hemorrhagic shock study using 28-day mortality as the primary endpoint. Mortality data were primarily analyzed using the TRISS method and a nonblinded clinical review, followed by an independent Pennsylvania Trauma Outcome Study (PTOS)-derived probability of survival analyses. Finally, a trauma expert conducted a blinded clinical review of cases incorrectly predicted by these PTOS analyses. **RESULTS:** More of the DCLHb patients predicted to survive using TRISS actually died than in the control subgroup (24% vs. 3%,  $p < 0.002$ ). Nonblinded clinical review noted that 72% of the patients who died had prior traumatic arrest, a presenting Glasgow Coma Scale score of 3, or a base deficit  $> 15$  mEq/L. DCLHb patients predicted to survive using PTOS also more often died than did control patients (30% vs. 8%,  $p < 0.04$ ). Blinded clinical review determined that 94% of the deaths were clinically justified. Both the TRISS and the PTOS models gave an adjusted mortality relative risk of 2.3, similar to the unadjusted risk data. **CONCLUSION:** Mortality analysis in this shock study involved both clinical case reviews and mortality prediction models. Despite the observation that nearly all of the deaths were clinically justified, the TRISS and PTOS models demonstrated excess unpredicted deaths in the DCLHb subgroup. A combined process, using both mortality prediction models and clinical case reviews, is useful in trauma studies that use a mortality endpoint.

**Gibson JB, Maxwell RA, Schweitzer JB, Fabian TC, Proctor KG. Resuscitation from severe hemorrhagic shock after traumatic brain injury using saline, shed blood, or a blood substitute. *Shock.* 2002 Mar;17(3):234-44.**

The original purpose of this study was to compare initial resuscitation of hemorrhagic hypotension after traumatic brain injury (TBI) with saline and shed blood. Based on those results, the protocol was modified and saline was compared to a blood substitute, diaspirin cross-linked hemoglobin (DCLHb). Two series of experiments were performed in anesthetized and mechanically ventilated ( $\text{FiO}_2 = 0.4$ ) pigs (35-45 kg). In Series 1, fluid percussion TBI (6-8 ATM) was followed by a 30% hemorrhage. At 120 min post-TBI, initial resuscitation consisted of either shed blood ( $n = 7$ ) or a bolus of 3x shed blood volume as saline ( $n = 13$ ). Saline supplements were then administered to all pigs to maintain a systolic arterial blood pressure (SAP) of  $> 100$  mmHg and a heart rate (HR) of  $< 110$  beats/min. In Series 2, TBI (4-5 ATM) was followed by a 35% hemorrhage. At 60 min post-TBI, initial resuscitation consisted of either 500 mL of DCLHb ( $n = 6$ ) or 500 mL of saline ( $n = 5$ ). This was followed by saline supplements to all pigs to maintain a SAP of  $> 100$  mmHg and a HR of  $< 110$  beats/min. In Series 1, most systemic markers of resuscitation (e.g., SAP, HR, cardiac output, filling pressures, lactate, etc.) were normalized, but there were 0/7 vs. 5/13 deaths within 5 h ( $P = 0.058$ ) with blood vs. saline. At constant arterial  $\text{O}_2$  saturation ( $\text{SaO}_2$ ), mixed venous  $\text{O}_2$  saturation ( $\text{SvO}_2$ ), cerebral perfusion pressure (CPP), and cerebral venous  $\text{O}_2$  saturation ( $\text{ScvO}_2$ ) were all higher, intracranial pressure (ICP) was lower, and  $\text{CO}_2$  reactivity was preserved with blood vs. saline (all  $P <$

0.05). In Series 2, SAP, ICP, CPP, and lactate were higher with DCLHb vs. saline (all  $P < 0.05$ ). Cardiac output was lower even though filling pressure was markedly elevated with DCLHb vs. saline (both  $P < 0.05$ ). Neither SvO<sub>2</sub> nor cerebrovascular CO<sub>2</sub> reactivity were improved, and ScvO<sub>2</sub> was lower with DCLHb vs. saline ( $P < 0.05$ ). All survived at least 72 h with neuropathologic changes that included sub-arachnoid hemorrhage, midline cerebellar necrosis, and diffuse axonal injury. These changes were similar with DCLHb vs. saline. Thus, whole blood was more effective than saline for resuscitation of TBI, whereas DCLHb was no more, and according to many variables, less effective than saline resuscitation. These experimental results are comparable to those in a recent multicenter trial using DCLHb for the treatment of severe traumatic shock. Further investigations in similar experimental models might provide some plausible explanations why DCLHb unexpectedly increased mortality in patients.

**Arnoldo BD, Minei JP. Potential of hemoglobin-based oxygen carriers in trauma patients. *Current Opinion in Critical Care*. 2001 Dec;7(6):431-6. Review.**

Injured patients have a unique requirement for early blood transfusion. A product that can be used in the prehospital setting that adequately carries and delivers oxygen to peripheral tissues would potentially be life saving for severely injured patients. Allogeneic blood is not the ideal agent in the pre-hospital setting. Present limitations in the allogeneic blood supply include the need for cross-matching, refrigeration, marginal supply, transfusion reactions, infectious disease transmission and immunomodulation increasing the risk of organ dysfunction after transfusion. Hemoglobin-based oxygen carriers have been under present development for the last 25 years. These compounds use either human or bovine hemoglobin that is then chemically altered to improve safety. These compounds exhibit many desirable characteristics that make them potential therapeutic agents in the treatment of the injured patient. These compounds do not need to be cross-matched, have favorable oxygen dissociation characteristics, long half lives, do not transmit disease, appear to be less immunoreactive than blood and theoretically can be used in the pre-hospital setting as a low volume oxygen carrying solution without need for refrigeration. There are at least three agents presently under development that use different techniques to alter the basic hemoglobin tetramer. While there is no FDA approved hemoglobin-based oxygen carrier approved for use in injured patients at this writing, phase III studies are currently either underway or being developed. There is high likelihood that one or more of these agents will be approved for clinical use in the near future.

**DCLHb Traumatic Hemorrhagic Shock Study Group. 1999. Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock: a randomized controlled efficacy trial. *JAMA*. 1999 Nov 17;282(19):1857-64.**

Severe, uncompensated, traumatic hemorrhagic shock causes significant morbidity and mortality, but resuscitation with an oxygen-carrying fluid might improve patient outcomes. **OBJECTIVE:** To determine if the infusion of up to 1000 mL of diaspirin cross-linked hemoglobin (DCLHb) during the initial hospital resuscitation could reduce 28-day mortality in traumatic hemorrhagic shock patients. **DESIGN AND SETTING:** Multicenter, randomized, controlled, single-blinded efficacy trial conducted between February 1997 and January 1998 at 18 US trauma centers selected for their high volume of critically injured trauma patients, but 1 did not enroll patients. **PATIENTS:** A total of 112 patients with traumatic hemorrhagic shock and unstable vital signs or a critical base deficit, who had a mean (SD) patient age of 39 (20) years. Of the infused patients, 79% were male and 56% were white. An exception to informed consent was used when necessary. **INTERVENTION:** All patients were to be infused with 500 mL of DCLHb or saline solution. Critically ill patients who still met entry criteria could have received up to an additional 500 mL during the 1-hour infusion period. **MAIN OUTCOME MEASURES:** Twenty-eight day mortality, 28-day morbidity, 48-hour mortality, and 24-hour lactate levels. **RESULTS:** Of the 112 patients, 98 (88%) were infused with DCLHb or saline solution. At 28 days, 24 (46%) of the 52 patients infused with DCLHb died, and 8 (17%) of the 46 patients infused with the saline solution died ( $P = .003$ ). At 48 hours, 20 (38%) of the 52 patients infused with DCLHb died and 7 (15%) of the 46 patients infused with the saline solution died ( $P = .01$ ). The 28-day morbidity rate, as measured by the multiple organ dysfunction score, was 72% higher in the DCLHb group ( $P = .03$ ). There was no difference in adverse event rates or the 24-hour lactate levels.



CONCLUSIONS: Mortality was higher for patients treated with DCLHb. Although further analysis should investigate whether the mortality difference was solely due to a direct treatment effect or to other factors, DCLHb does not appear to be an effective resuscitation fluid.

## **2. The Ethics and Law of Emergency Research (general)**

**Proceedings of the 2005 Academic Emergency Medicine Consensus Conference on Ethical Conduct of Resuscitation Research. New York City, New York, USA, May 21, 2005.** *Academic Emergency Medicine*. 2005 Nov; 12(11):1015-137.

This issue of *Academic Emergency Medicine* is devoted to Ethical Conduct of Resuscitation Research including the proceedings of this year's Consensus Conference held in New York City on May 21, 2005. The conference focused on questions surrounding the performance of resuscitation research using the 1996 federal regulations jointly published by the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) and known as the Final Rule.<sup>1</sup> Researchers have raised concerns about their ability to perform resuscitation research, while at the same time, questions have been raised about the adequacy of the protection for human subjects. The conference served as a mechanism to accomplish the following goals: 1) explore the legitimacy of these concerns, 2) discuss potential solutions to the barriers to performing resuscitation research, 3) develop education for researchers and the regulatory community regarding design and execution of resuscitation research using the Final Rule, and 4) formulate a research agenda for studying the impact of the Final Rule on current resuscitation research and for developing effective strategies for implementation of various aspects of the Final Rule.

Richardson LD. **The ethics of research without consent in emergency situations.** *Mount Sinai Journal of Medicine*. 2005 Jul;72(4):242-9.

In 1996, the federal government published regulations that allow investigators to obtain a waiver of informed consent for emergency research when certain very specific criteria are met. The participants must be unable to give consent as a result of their medical condition, and the intervention involved in the research must be administered before consent from the participants' legally authorized representative is feasible. These regulations require that a number of special protections be provided whenever such a waiver is obtained. Before the study is performed, there must be "community consultation" and "public disclosure." The regulations leave the specific form and extent of these activities to the discretion of the Institutional Review Board granting the waiver of informed consent and the investigator conducting the study. The author reviews the development of these regulations, often referred to as "The Final Rule," the ethical basis for the waiver, and the specific provisions of the federal regulations that govern research without consent in emergency situations. Reactions of proponents, critics and the lay public are discussed.

Kompanje EJ, Maas AI, Hilhorst MT, Sliker FJ, Teasdale GM. **Ethical considerations on consent procedures for emergency research in severe and moderate traumatic brain injury.** *Acta Neurochirurgica (Wien)*. 2005 Jun;147(6):633-9; discussion 639-40. Epub 2005 Apr 7. Review.

Therapeutic trials in TBI are subject to principles of Good Clinical Practice (GCP), to national legislation, and to international and European ethical concepts and regulations [e.g. 13]. The guiding principles underlying these investigations of treatment are respect for autonomy of research subjects, protection against discomfort, risk, harm and exploitation and the prospect of some benefit. Patients with significant TBI are mentally incapacitated, thus prohibiting obtaining consent directly from the subject. Various approaches to consent procedures are used as surrogate to subject consent: proxy consent, consent by an

independent physician and waiver of consent. These approaches are reviewed. A questionnaire soliciting opinions was mailed to 148 EBIC (European Brain Injury Consortium) associated neuro-trauma centers in 19 European countries. 48% respondents believe that relatives were not able to make a balanced decision, 72% believed that consent procedures are a significant factor causing decrease in enrollment rate and 83% stated that consent procedures delay initiation of study treatment, resulting in possible harm if the agent has shown to be effective. 64% of the respondents considered TBI an emergency situation in which clinical research could be initiated under the emergency exception for consent. In new European legislation, emergency research under waiver of consent is not permitted. Nevertheless, we consider that randomising patients with TBI into carefully evaluated trial protocols without prior consent may be considered ethically justified.

**Raju TN. Waiver of informed consent for emergency research and community disclosures and consultations.** *Journal of Investigative Medicine*. 2004 Mar;52(2):109-12. Review.

**Dix ES, Esposito D, Spinoso F, Olson N, Chapman S. Implementation of community consultation for waiver of informed consent in emergency research: one Institutional Review Board's experience.** *Journal of Investigative Medicine*. 2004 Mar;52(2):113-6.

**BACKGROUND:** This article describes how one Institutional Review Board (IRB) chose to implement the issue of waiver of consent for a research study involving brain trauma victims brought to an emergency department. **METHODS:** Presentations were conducted in the state of Mississippi among cultural and ethnic groups representative of Mississippi's demographic composition. Individuals from the neurotrauma research team, including neurosurgeons and nurse study coordinators, conducted all of the presentations. One IRB member served as an objective "community liaison" and attended all presentations. This individual administered evaluation forms to attendees that measured their levels of comprehension and acceptance for the use of waiver of consent in the brain trauma study. **RESULTS:** All of the 137 attendees in 7 community consultation meetings gave their approval for the use of "waiver of consent." Continued community consultations are planned for the duration of the brain trauma study. **CONCLUSION:** Based on our experience, we conclude that in collaborating with local IRBs, research teams can successfully develop strategies for obtaining "acceptable community consultations" as required by regulatory mandates. We suggest that standardized community consultation guidelines be developed for obtaining waivers of informed consent in emergency research. Such criteria should form the basis for local IRBs to obtain their respective community consultations.

**Vanpee D, Gillet JB, Dupuis M. Clinical trials in an emergency setting: implications from the fifth version of the Declaration of Helsinki.** *Journal of Emergency Medicine*. 2004 Jan;26(1):127-31.

Everybody agrees that research is crucial to improve the quality of emergency care. Consent of human subjects for participation in research requires that they fully understand their role and risk, not be coerced, and be allowed to withdraw at any time without penalty. In an emergency situation, informed consent is not always possible but the need for good research data is very high. Here is the ethical difficulty, and a real conflict of values: a population that might ultimately benefit from research cannot consent to the research and are thus excluded from the potential therapeutical advances. Patients at high risk of morbidity or death, with cardiac arrest, shock, head injury, or altered mental status, are evidently incapable of providing an adequate consent, but nevertheless are often in the greatest need of innovative therapy and might be willing to assume some risk for potential benefit. In an attempt to resolve this dilemma, the new version of the Declaration of Helsinki presents updated requirements for the waiver of informed consent and the protection of human subjects in emergency research.

**Biros MH. Research without consent: current status, 2003.** *Annals of Emergency Medicine*. 2003 Oct;42(4):550-64.

In November 1996, regulations developed by the US Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS) went into effect to allow certain emergency and resuscitation human subjects research to proceed without prospective informed consent. These new regulations brought harmonization to the requirements of the 2 federal agencies charged with research oversight and ended a moratorium that had essentially shut down resuscitation research for almost 4 years. However, the FDA's emergency exception from informed consent and the HHS's waiver of informed consent have been used infrequently. Many perceived obstacles to implementation of the regulations have been described, including the additional regulatory burden for investigators and institutional review boards, the extra expense and time required to adequately fulfill the regulatory requirements, and the reluctance of institutional review boards to allow these studies to move forward because of concerns about potential legal ramifications. Regardless of the arguments advanced, these regulations are essentially the only current regulatory options that have been provided for research without consent. This article presents a brief history of the development of the FDA's Final Rule, a summary of its requirements and its use so far, and suggestions for its implementation. Some strategies to allow the resuscitation research community to suggest fine tuning of the regulations are suggested in hopes that research requiring an exception from informed consent is allowed to proceed in a manner acceptable to regulators, is stringent in patient protection, and yet is sensitive to the practical aspects of performing resuscitation research.

**McClure KB, DeIorio NM, Gunnels MD, Ochsner MJ, Biros MH, Schmidt TA. Attitudes of emergency department patients and visitors regarding emergency exception from informed consent in resuscitation research, community consultation, and public notification.** *Academic Emergency Medicine*. 2003 Apr;10(4):352-9. Erratum in: *Academic Emergency Medicine*. 2003 Jun;10(6):690.

**OBJECTIVE:** To assess public views on emergency exception to informed consent in resuscitation research, public awareness of such studies, and effective methods of community consultation and public notification. **METHODS:** A face-to-face survey was conducted in two academic Level I trauma center emergency departments (EDs) in Oregon and Minnesota from June through August 2001. **RESULTS:** Five hundred thirty people completed the survey, with an 82% response rate. The mean age of the respondents was 41 years (range 18-95) with a standard deviation of 14.5; 46% were female and 64% white. Most (88%) believed that research subjects should be informed prior to being enrolled, while 49% believed enrolling patients without prior consent in an emergency situation would be acceptable and 70% (369) would not object to be entered into such a study without providing prospective informed consent. Informing and consulting the community as a substitute for patient consent in emergency research was thought to be reasonable by 45% of the respondents. Most respondents would prefer to be informed about a study using emergency exception from informed consent by radio and television media (42%). Two hundred fifty-eight respondents (49%) stated they would attend a community meeting; the less educated were more likely to attend than those with college degrees (OR = 0.53; 95% CI = 0.33 to 0.85, p = 0.008). However, only 5% knew of ongoing studies in their community using emergency exception from informed consent. **CONCLUSIONS:** Most respondents disagreed with foregoing prospective informed consent for research participation even in emergency situations; however, many would be willing to participate in studies using emergency exception from informed consent. Most respondents would not attend community meetings, and would prefer to rely upon the media for information. Very few were aware of emergency exception from informed consent studies in their community. This suggests that current methods of community notification may not be effective.

**Mann H. Clinical trial protocols: agreements between the FDA and industrial sponsors.** *Lancet*. 2002 Nov 2; 360(9343):1345-6.

Baren JM, Anicetti JP, Ledesma S, Biros MH, Mahabee-Gittens M, Lewis RJ. **An approach to community consultation prior to initiating an emergency research study incorporating a waiver of informed consent.** *Academic Emergency Medicine*. 1999 Dec;6(12):1210-5.

### **3. Articles on the Ethics and Law of Emergency Research Involving Blood**

Kipnis K, King NMP, Nelson RM. **Trials and Errors: Barriers to Oversight of Research Conducted under the Emergency Research Consent Waiver.** *IRB: Ethics & Human Research* 28, No. 2 (2006): 16-19.

Lewis RJ, Berry DA, Cryer H 3rd, Fost N, Krome R, Washington GR, Houghton J, Blue JW, Bechhofer R, Cook T, Fisher M. **Monitoring a clinical trial conducted under the Food and Drug Administration regulations allowing a waiver of prospective informed consent: the diaspirin cross-linked hemoglobin traumatic hemorrhagic shock efficacy trial.** *Annals of Emergency Medicine*. 2001 Oct; 38(4):397-404.

In 1996, the US Food and Drug Administration (FDA) enacted Rule 21 CFR section 50.24, which allows a narrow exception to the requirement for prospective informed consent from human research subjects in clinical trials investigating potentially beneficial therapies for acute, life-threatening conditions. The first clinical trial to be conducted under this rule was sponsored by Baxter Healthcare Corporation and approved by the FDA on November 21, 1996. This large, multicenter, randomized clinical trial was designed to compare the addition of diaspirin cross-linked hemoglobin (DCLHb) with standard care in the initial resuscitation of adults experiencing severe, uncompensated, traumatic hemorrhagic shock. Before the first planned interim analysis of the data, review of fatal adverse events revealed an imbalance in mortality between the 2 treatment groups. The Data Monitoring Committee (DMC) recommended suspension of patient enrollment 24 days later. Additional data collection and analyses confirmed the excess number of deaths in patients treated with DCLHb but failed to reveal the cause of these deaths. The trial was formally terminated after only 112 of the planned 850 patients had been enrolled. We review the events leading up to and the rationale behind the DMC recommendations for suspension of patient enrollment and trial termination. Although the DCLHb trial was unsuccessful in achieving its goals, the monitoring process worked well. Emergency research was facilitated by DMC oversight, and the interests of research subjects were protected by the actions of the DMC.

Sloan EP, Nagy K, Barrett J. **A proposed consent process in studies that use an exception to informed consent.** *Academic Emergency Medicine*. 1999 Dec; 6(12):1283-91. Review.

Federal regulations allow an exception to informed consent when it is not feasible to obtain informed consent in certain emergency research circumstances. A multicenter, randomized, single-blinded, normal saline procedure-controlled efficacy trial of diaspirin cross-linked hemoglobin (DCLHb) in acute traumatic hemorrhagic shock was conducted. The study intended to include 850 of the most severely injured trauma patients with hemorrhage and persistent hypoperfusion as demonstrated by vital signs suggestive of vascular collapse or a base deficit that signified prolonged hypoperfusion. It was anticipated that some patients would be unable to provide informed consent, and that identification and availability of some patients' legally authorized representatives (LARs) would be unlikely within the therapeutic window of the intervention. Each participating institution therefore developed a process to implement exception to informed consent. Each hospital's proposed process was reviewed by the institutional review board, the

sponsor, the FDA, and the study's data monitoring committee chair. The goal was the development of local implementation processes by which the best interests of patients and their families could be fulfilled using prospective informed consent, the exception to informed consent, and consent to continue in emergency research, as appropriate for each individual patient. This paper describes the proposed implementation method developed for Cook County Hospital. It includes several important features, 1) prospective informed consent by the patient, when feasible; 2) the ability of the patient to decline participation, even when deemed incompetent to provide prospective informed consent; 3) prospective consent by the family/LAR, when feasible; 4) the use of a scripted abbreviated consent by the patient family/ LAR in life-threatening situations when it is possible only to briefly discuss the research being conducted; 5) independent approval for the use of the consent exception by a second physician immediately prior to patient enrollment; 6) the repeated use of consent to continue (both for the family/LAR and by the patient) when an exception to consent has been utilized; and 7) ongoing review of the informed consent process on a case-by-case basis by the institution's scientific review committee. The authors believe this proposed informed consent process maximizes the communication between investigators, patients and their proxies, and the institution's scientific review committee. Multiple mechanisms exist that allow for consent to be provided or declined, both prior to and after enrollment in the research protocol. The ongoing immediate review of the process allows for process enhancements to be made as needed.

Sloan EP, Koenigsberg M, Houghton J, Gens D, Cipolle M, Runge J, Mallory MN, Rodman G Jr. **The informed consent process and the use of the exception to informed consent in the clinical trial of diaspirin cross-linked hemoglobin (DCLHb) in severe traumatic hemorrhagic shock.** DCLHb Traumatic Hemorrhagic Shock study group. *Academic Emergency Medicine*. 1999 Dec; 6(12):1203-9.

In the clinical trial of diaspirin cross-linked hemoglobin (DCLHb), optimal therapy required the immediate enrollment of patients with severe, uncompensated, traumatic hemorrhagic shock. When it was not feasible to obtain prospective consent, an exception to informed consent was used according to FDA regulation 21 CFR 50.24. **OBJECTIVES:** To examine the informed consent process and the use of the consent exception and consent to continue (CTC), and to describe the patients for whom this process was used. **METHODS:** This was a multicenter, randomized, controlled, single-blinded efficacy trial of DCLHb as an adjunct to standard therapy in the treatment of severe, traumatic hemorrhagic shock. Patients with unstable vital signs or a critical base deficit were treated, with a primary study endpoint of 28-day mortality. **RESULTS:** During the 11-month study period, 112 patients were randomized in 18 U.S. trauma centers, and data from 98 of the infused patients were analyzed. Prospective consent was obtained from two patients, three family members, and one legally authorized representative (LAR) (6%). Consent to continue was requested for 89 patients (89%), and full participation was granted for 87 of these patients (98%). Consent to continue was provided by 54 (98%) of the 55 patients approached. The mean number of days for family/LAR CTC was 1.1 +/-3.8 days, and 50% of the time it was obtained on the day of study enrollment. Patient CTC was obtained in an average of 13 +/- 23 days, with a median of four days. Patients treated in this protocol were more likely to have sustained penetrating trauma than the overall trauma patient population treated in these trauma centers (44% vs 21%,  $p = 0.002$ ). **CONCLUSIONS:** Informed consent in this study of an emergent therapy most often involved the use of the consent exception and consent to continue, the latter of which occurred in a timely manner. Nearly all of those who were approached for CTC approved full participation in the study, suggesting acceptance of the process outlined in the new regulations. Patients treated in a hemorrhagic shock clinical trial may differ from the general trauma patient population.