



July 17, 1997

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Docket Number 95S-0158  
Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12420 Parklawn Dr. rm. 1-23  
Rockville, MD 20857

**RE: Investigational New Drug Application #6859**

Dear Sir/Madam:

In accordance with 21 CFR §312.54 we are enclosing copies of information concerning research involving an exception to informed consent. This includes information that has been publicly disclosed by the IRB at Methodist Hospital of Indiana, Indianapolis, IN, the IRB of Washington Hospital Center, Washington D.C., and additional information from Lehigh Valley Hospital, Allentown, PA.

The information for Methodist Hospital includes the agenda for Grand Rounds (Attachment 1), and the agenda for the EM Conference (Attachment 2) presented by the Coordinating Investigator of the study on May 7, 1997; the protocol synopsis that was distributed at various internal staff meetings and sent to various community and state members and officials (Attachment 3); a communication entitled *Frequently Asked Questions About DCLHb* that was distributed at various internal staff meetings and community meetings, and was also sent to various community and state members (Attachment 4); an article that appeared in an internal hospital newspaper, *the Clarian*, on May 27, 1997 (Attachment 5); an advertisement for an informational session for staff that was posted in the hospital and also appeared in an internal hospital newspaper, *the Clarian*, on May 27 and June 2, 1997 (Attachment 6); a news release (Attachment 7) and fact sheet (Attachment 8) that was sent to the local press on May 29, 1997; an article that appeared in both the morning and evening edition of a local newspaper, *The Indianapolis Star*, on May 31, 1997 (Attachment 9); an editorial that appeared in the morning edition of a local newspaper, *The Indianapolis Star*, on June 9, 1997 (Attachment 10); posters announcing Town Hall Meetings (Attachment 11) and an advertisement announcing Town Hall Meetings which appeared in a local newspaper, *The Indianapolis Star*, on June 1, 1997 (Attachment 12), and June 8, 1997

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(Attachment 13); the agenda for the Town Hall Meetings that were held on June 3, 4, 5, and 9, 1997 (Attachment 14); a letter that was sent to every Hospital in Indiana on May 22, 1997 (Attachment 15); a letter that was sent on June 2, 1997, to the EMS Coalition, the Chief of the Indianapolis Fire Department, the Chief of Police, the Director of the Department of Public Safety, and the Marion County Sheriff (Attachment 16); a letter (Attachment 17) and a copy of the FDA regulations regarding Exception to Informed Consent (Attachment 18) that were sent on June 2, 1997 to the Mayor of Indianapolis, the Commissioner of the State Board of Health, the Public Health Director of the Marion County Health Department, the Attorney General of Indiana, the Marion County Prosecutor, the Forensic Pathologist of Indiana University Medical Center, and the Marion County Coroner; a letter that was sent to the Superintendent of the Indiana State Police on June 2, 1997 (Attachment 19); and a summary of questions that were asked by a local radio station, WIBC, on June 4, 1997, and broadcast on June 5, 1997, and also the week of June 10, 1997 (Attachment 20).

Based on information received from the clinical site, the investigator and IRB of Methodist Hospital achieved community consultation by presenting a summary of the study to community members in several Town Hall Meetings (Attachments 4, 11, 12, 13, 14). In addition, letters describing the study, as well as the protocol synopsis and a copy of the FDA regulations regarding Exception to Informed Consent were sent to various community and state members and officials (Attachments 3, 15, 16, 17, 18). Finally, a toll-free number was established to answer any concerns from the public.

The information for Washington Hospital Center includes press releases from January 31, 1997 (Attachment 21) and March 20, 1997 (Attachment 22); a transcript from a local television news broadcast, WJLA-TV (ABC), broadcast on March 20, 1997 (Attachment 23); the agenda (Attachment 24) and minutes (Attachment 25) of a Community Relations Council Meeting held on April 24, 1997; a summary of a local radio interview with the principal investigator and an interview for *Healthline* (Attachment 26); an article that appeared in a local newspaper, *The Washington Times* on May 26, 1997 (Attachment 27); and an advertisement that appeared on June 26, 1997, in local newspapers, *The Washington Informer* (Attachment 28), *The Washington Post* (Attachment 29), and *Il Pregonano* (same information; not included).

Based on information received from the clinical site, the investigator and IRB of Washington Hospital Center achieved community consultation by presenting a summary of the study to community representatives at a Community Meeting (Attachments 24, 25). Additionally, discussions of DCLHb and the study were broadcast on local television and radio stations (Attachments 23, 26), and an advertisement providing information and address, phone and fax number for questions or concerns was provided in a variety of local newspapers (Attachment 28, 29).

Dockets Management Branch (HFA-305)  
July 17, 1997

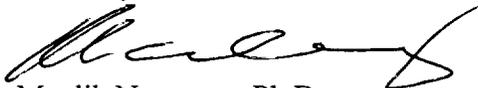
IND # 6859  
Page Three

Additional information from Lehigh Valley Hospital includes an article that appeared in a hospital publication, *Healthy You*, in the March/April, 1997 edition (Attachment 30).

In accordance with 21 CFR §312.54, this information is also being submitted to the IND file.

If there are any questions concerning this information, please contact me at (847)270-5313.

Sincerely,



Maulik Nanavaty, Ph.D.  
Director Regulatory Affairs  
Blood Substitutes Program



Overview of Grand Rounds presentation at Methodist Hospital- May 7, 1997

Introduction to DCLHb- Ed Sloan, MD, MPH (presenter)

- Chemical structure- cross-linked to stabilize
- Hemoglobin based oxygen carrier
- Pressor/perfusion properties

Preclinical Overview

- Product properties seen in preclinical studies including increases mean arterial pressure, restores base deficit, restores lactate levels, restores subcutaneous PO<sub>2</sub>, restores mucosal PO<sub>2</sub>, reduces bacterial translocation, increases oxygen consumption, reduces mortality and perfusion properties
- Review of specific data from preclinical studies that support each of the above

Hemorrhagic Hypovolemic Shock Study Overview (completed study)

- Study design
- Summary of patient population
- Summary of safety findings- no increase rate of complications or adverse events
- Efficacy findings- patient population not sufficient to determine efficacy

Traumatic Hemorrhagic Shock Study Overview

- Introduction to trauma and the impact on society
- History of protocol development
- Study design
- Patient care- all standard therapies will be provided
- Study inclusion/exclusion criteria
- Timelines mandated by protocol
- Dosing and infusing
- Blinding of study, investigators blinded prior to randomization, not blinded during infusion
- Endpoints and analyses- 28 day mortality, morbidity using the MOD score, 48 hour mortality
- Laboratory issues
- Exception from informed consent issues and consent to continue
- Role of the IRB- community consultation and public disclosure

Overview of Grand Rounds presentation at Methodist Hospital- May 7, 1997 (cont.)

Hemoglobin Based Oxygen Carriers (HBOCs)

Old paradigm- blood substitutes

New paradigm- hemoglobin-based oxygen carriers

HBOCs potential uses- trauma, blood loss, surgery, MI, stroke, cancer, radiation therapy, cardiopulmonary bypass, sepsis, dialysis, sickle cell disease, anemia

Summary

Trauma important issue

Study to determine if DCLHb will improve survival



Overview of EM Conference presentation- May 7, 1997

Ed Sloan, MD, MPH- presenter

Overview of the regulations for an exception from informed consent

Principles behind the regulations

Basis for allowing a waiver of consent

Process of community consultation and public disclosure

Process of consenting patients in the THS study



03 October 1996

Protocol Synopsis**“The Efficacy Trial of Diaspirin Cross-linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock”**Introduction

Death from trauma frequently results from shock that is refractory to resuscitation efforts. These efforts typically involve rapid infusions of large volumes of crystalloid solutions. This standard of therapy has been brought into question by recent clinical studies utilizing small volumes of hypertonic saline-Dextran solution (Mattox et al. 1991, Ann Surg 213:482-91), or no volume replacement until definitive surgical treatment (Bickell et al. 1994, N Eng J Med 331:1105-1109).

Trauma-related mortality has been correlated with the magnitude of base deficit. According to Siegel et al. (Arch Surg 1990, 125:498-508), a base deficit of 11.8 mmol/L predicts a mortality of 50% in trauma patients presenting with pelvic fractures or blunt liver trauma. Rutherford et al. (J Trauma 1992, 33:417-423) reported a mortality rate over 40% in trauma patients with base deficits in excess of 15 mmol/L. This study of 3791 trauma patients also showed a sharp, corresponding rise in mortality rates from 20% to 40% over the base deficit range of 10 to 15 mmol/L.

The above findings suggest that the current practice of restoring blood pressure through large volume crystalloid infusion may be suboptimal in traumatic hemorrhagic shock patients. These traumatic shock patients, especially those with large base deficits, are at greatest risk, and warrant being studied with a controlled clinical trial with a low volume pressor/perfusion agent such as DCLHb.

Initial DCLHb Hemorrhagic Shock Trial

The initial prospective, randomized, escalating dose clinical trial of DCLHb in hemorrhagic shock studied the infusion of normal saline (NS) or DCLHb in class II-IV shock patients within four hours of the shock episode. The trial was divided into three dose ranges, 50 mL (71 mg/kg), 100 mL (143 mg/kg), and 200 mL (286 mg/kg). Each dose included approximately 40 patients (20 NS, 20 DCLHb). Patient enrollment for this clinical trial was completed in May 1995 with a total population of 139 patients, 71 (51%) of whom received DCLHb.

No increase in the rate of complications or toxicities in patients who received DCLHb were observed during the trial. Specifically, renal insufficiency and failure were not more common in DCLHb-treated patients. Overall mortality rates, complications and adverse event rates did not differ in the DCLHb and control groups. These findings, and findings from several other DCLHb trials at different doses (750-1200 mLs), suggest that DCLHb infusion will have a favorable risk/benefit profile in severely injured patients.

Study Design

This will be a multicenter, randomized, placebo-controlled (normal saline) study. Inclusion in this protocol will not interfere with the provision of any standard trauma therapy.

Primary Clinical Benefit Endpoint

- Clinically and statistically significant reduction in 28 day mortality.

Secondary Clinical Benefit Endpoint

- Clinically and statistically significant reduction in morbidity.
- Clinically and statistically significant reduction in 48 hour mortality.
- Clinically and statistically significant reduction in 24 hour lactate levels.

Patient Population

The study population will be a small subset of trauma patients with persistent, severe, hypoperfusion despite aggressive pre-hospital therapy. To properly investigate the mortality and morbidity outcomes in this protocol, 500 to 1000 mL DCLHb or the saline control will begin being infused no later than 30 minutes after meeting the entry criteria and within 60 minutes of presentation to the emergency department in approximately 850 patients meeting the following inclusion criteria:

1. Males or females 18 years of age or older
2. Evidence of hemorrhage
3. Tissue hypoxia and cellular hypoperfusion shown by:
  - Systolic blood pressure  $\leq 90$  and pulse  $\geq 120$  or,
  - Systolic blood pressure  $\leq 90$  and pulse  $< 60$  with a pre-terminal rhythm (junctional or idioventricular) or,
  - Base deficit of 15 mmol/L or worse

Patients will be excluded from the study by the following exclusion criteria:

1. Age  $< 18$  years
2. Known pregnancy
3. Pulseless traumatic arrest during hospitalization
4. Imminent death precludes resuscitation efforts
5. Isolated head trauma, penetrating or blunt
6. Combined multisystem and head trauma with clinical findings consistent with significant mass effect (e.g., severe coma, lateralizing signs, posturing, or pupillary dilatation secondary to uncal herniation)
7. Hospitalization  $> 60$  minutes prior to infusion
8. Known objection to the use of blood, blood products
9. Known injury time  $> 4$  hours prior to infusion

Statistical Approach

Approximately 850 patients will be needed to show a 25% reduction in mortality (i.e., from 40% to 30%). A Cox proportional hazards model will be used to determine the impact of DCLHb on mortality while adjusting for demographic and pre-treatment covariables documented as predictors of mortality. Interim monitoring will occur at 10%, 25%, 50%, 75% and the final analysis at 100% enrollment of the 850 patients.

Safety Monitoring

An independent Data Monitoring Committee (members not affiliated with Baxter Healthcare) will be established by the sponsor. Ongoing safety monitoring will be performed by this committee during the enrollment of study patients. If major safety concerns arise, the study can be amended or put on hold until these concerns are addressed.

Informed Consent

The consent procedures followed in the protocol will follow 21 CFR 50.24 "Exception from informed consent requirements for emergency research". These regulations will be utilized based on the favorable risk/benefit profile of DCLHb and the frequent lack of feasibility in obtaining prospective informed consent in this patient population.



## Frequently Asked Questions About DCLHb™ Methodist Hospital Of Indiana, Inc.

### ***Why is this trial being performed?***

Critically injured patients frequently arrive in the Emergency Department in shock from significant blood loss. Despite the best care medicine has to offer today, as many as 40% of these critically injured patients will die from their injuries. Animal and human clinical studies suggest that DCLHb™ may improve the chance of survival following severe blood loss. The solution has the greatest chance of improving survival and reducing complications when it is given immediately after the beginning of severe shock and bleeding.

### ***What is DCLHb™?***

DCLHb™ is a purified hemoglobin solution prepared from units of human red blood cells which have been donated by healthy volunteers. The hemoglobin (the part of the blood that carries oxygen) is extracted from the red blood cells and placed into a solution containing Diaspirin. This solution is heated and filtered similar to a pasteurization process. The blood used to make the experimental DCLHb™ solution has been tested and found negative for the viruses that cause hepatitis and AIDS. It is as safe as human albumin products.

DCLHb™ can be given immediately to a patient with any blood type. Cross matching is not required. DCLHb™ may restore blood pressure, increase blood flow to vital organs, and carry oxygen to cells and tissues. All three of these actions can be helpful in reducing the mortality and complications from severe shock.

### ***Can DCLHb™ be given to Jehovah Witness patients?***

No. Since DCLHb™ is made from human blood, it will not be administered to patients if it is known that their religious beliefs forbid blood transfusions. People who will not accept blood transfusions usually carry a card in their wallet.

### ***Does DCLHb™ replace the need for blood transfusions?***

No. DCLHb™ will be administered in addition to all standard therapies used to resuscitate a critically injured trauma patient. Standard therapies may include immediate use of blood transfusions, fluid therapies, and surgical intervention.

### ***What are the side effects of DCLHb™?***

DCLHb™ has been studied in randomized clinical trials involving more than 700 patients over a four year period to evaluate its effects. Of the approximately 350 patients who have received the solution, a few temporary side effects were noted. These included temporary changes in some lab test results, a temporary and harmless yellowing of the skin (unrelated to liver damage), temporary red color of the urine due to the red color of the DCLHb™ solution, nausea, and back, abdominal, and muscle pain. The yellow color is due to the normal body mechanism of breaking down the hemoglobin into components the body can use to make new red blood cells. One component, bilirubin is responsible for the temporary yellow skin color. Blood pressure may be elevated following infusion of the solution, but this may be beneficial to patients in shock whose blood pressure is dangerously low.

All DCLHb™ solution will be gone from the body within 96 hours after the last infusion. The interference in lab values, yellow skin, and red color of urine is expected to clear within 96 hours.

### ***Which lab tests may have interference?***

The Methodist Laboratory has undergone extensive evaluation of all standard blood and urine lab with samples of DCLHb™ solution. The only three tests to have interference for the first 96 hours is the direct and indirect bilirubin and LDH. These tests are not routinely ordered for trauma patients in the first 96 hours.

### ***Who will be eligible to participate?***

We are hoping to enroll 20 trauma patients over the next 18 months. The study sponsor would like to enroll 850 patients from 40 Trauma Centers in the United States. Patients 18 years of age and older who meet entry criteria will be randomized to either receive the DCLHb™ solution or Normal Saline in addition to all standard trauma therapies.

An Independent Monitoring Committee will be reviewing patient data submitted by all the study sites throughout the trial. The investigators at Methodist Hospital will submit a report every six months to the Methodist Institutional Review Board.

### ***What is an Exception to Informed Consent and why was it necessary for this study?***

Patients eligible for this study are suffering from a catastrophic traumatic event and are often not able to give consent due to their medical condition. Because the onset of traumatic injury is sudden and unpredictable, a legally authorized representative may not be immediately available to provide consent for the patient. An exception from informed consent will only be utilized if the patient, a legal representative, or family member is unavailable to give consent and the DCLHb™ infusion must be started. The infusion needs to be started within 60 minutes of presentation to the emergency department. Time of injury to time of initiation of DCLHb™ cannot be longer than four hours.

The FDA, in cooperation with the National Institute of Health (NIH), issued regulations in November of 1996 that will allow for certain emergency research to be conducted with an exception from informed consent. The new regulations allow for a study to be conducted with an exception or waiver from the requirement for obtaining written informed consent only in those rare circumstances when the patient cannot consent and the nature of the patient's

medical condition requires immediate treatment. The study of DCLHb™ in the treatment of severe traumatic hemorrhagic shock meets the FDA criteria for an exception or waiver from informed consent.

The new FDA regulations clearly state that the Institutional Review Board ( IRB ) at a center participating in a study utilizing the exception to informed consent is responsible for ensuring the protection of the patients.

Additional protections include:

1. Consulting with the communities from which patients will be drawn.
2. Public disclosure of the study and its risks and expected benefits prior to starting the study.
3. Public disclosure of information after the study is completed to inform the community and researchers of the results of the study.
4. Establishing an independent data monitoring committee to exercise oversight of the study. Baxter Healthcare and ClinTrials Research Inc. have established an independent monitoring committee
5. If consent from the patient is not feasible and a legally authorized representative is not available, providing an opportunity, if feasible, for a family member to consider the patient's participation in the study.

The development of these regulations allows for the advancement of vital emergency research with careful attention to the protection of the rights and welfare of the patients who are enrolled in the experimental protocol. The FDA and NIH expect that the studies conducted under these rules will allow patients in certain life threatening situations, who are unable to give informed consent because of their condition, the chance to receive potentially lifesaving treatments. They also expect that these studies will increase the knowledge and improve the treatments currently used in emergency medical situations that have poor patient outcomes, despite optimal care.

The investigators will make every attempt possible to obtain consent from patients, their legal representatives, or family before DCLHb™ is given. All patients and family members will be completely informed of their participation as soon as possible. At all times, the patient or their representatives may decline further participation in the study.

***Is the patient charged for the DCLHb™?***

All the costs for the DCLHb™ solution, monitoring, and study specific laboratory studies are paid for by the study sponsor, Baxter Healthcare Corporation. All standard therapies and hospital charges will be billed to the patient's health insurance carrier.

***Who can I call for more information?***

A 1-800 - 833 - 2457 is available for the community to ask questions, state concerns, or request information about the protocol or consent process. All questions will receive a prompt response. Dr. George Rodman, Director of Trauma Services, is the Principal Investigator for the study

***How is this study being communicated to the community?***

Under the new FDA regulations for an "Exception to Informed Consent", we are informing the community about the study protocol, the benefits, the risks, and the Exception to Informed Consent. An article has been published in the Indianapolis Star & News and a press release will be sent to newspapers across the state. Four Town meetings have been scheduled for the first two weeks in June at all four of the Methodist Medical Plaza Centers. The community can call 1-800-833-2457 or write Methodist Hospital.

External communications include:

- Article in Indianapolis Star & News May 31.
- Town Meetings at each of the Methodist Medical Plaza Centers

East:

Tuesday, June 3 at 1800

North

Wednesday, June 4 at 1800

South  
Thursday, June 5 at 1700  
West

Monday, June 9 at 1630

- Jehovah Witness clergy
- Attorney General
- State Health Commissioner
- Marion County Health Department
- EMS Coalition
- State Emergency Management Agency
- Law enforcement officials
- State legislators and church leaders
- Health insurance companies
- Hospitals throughout the state

Methodist Hospital  
Trauma Service - B229  
I-65 at 21st Street PO Box 1367  
Indianapolis, Indiana 46206-1367

1-800-833-2457





# Cl<sup>the</sup>ararian

A publication for the employees, physicians and volunteers of Methodist, IU and Riley hospitals



BB-JND #6859-013

## Study to Test New Blood Solution

Methodist Hospital is participating in an international research study of a product that could dramatically affect the way severely injured patients are treated in the world's emergency rooms.

Methodist's Emergency Medicine and Trauma Center (EMTC) is one of 40 trauma centers studying whether a new blood solution called HemAssist can prevent deaths and reduce complications for patients in shock because of severe blood loss. The study has been approved by the U.S. Food and Drug Administration.

The product, which was developed by Baxter Healthcare Corp. of Deerfield, Ill., is a modified hemoglobin solution made from human red blood cells. Eventually, the new blood solution could be used in emergency situations that require blood transfu-

sions or injections of saline solutions.

"When patients are in shock because of severe bleeding, the loss of blood can damage or shut down vital organs such as lungs and kidneys," said Maureen Misinski, trauma program coordinator. "Blood transfusions bring desperately needed oxygen to such organs.

"However, in emergency situations when every second counts, it takes precious time to test and match a patient's blood type. If it proves to be effective, the new solution would eliminate much of the need to take time matching blood types."

In addition to saving lives and reducing complications, the solution could reduce the risk of infection and be available even when donated blood supplies are low.

Every standard emergency room

treatment will also be administered to all patients who receive the new solution.

The blood solution would be administered only to adults 18 and older. It will be used only for patients in shock from bleeding caused by chest and abdominal injuries. It will not be given to pregnant women or people with brain injuries. It will not be given on ambulances or on the Life Line helicopter.

Due to the speed required to administer emergency medical treatment, the FDA has waived patient consent requirements. Patients may receive the solution without prior consent, but will also receive all standard medical treatment. Patients and their family members will be informed of the study and given the opportunity to decline further participation.

The FDA requires Methodist to provide public notice about the study to potential patients. Therefore, community meetings will be conducted, explaining the study and the FDA's regulations for an Exception to Informed Consent.

The meetings will be at the following times and locations:

- June 3, 6 p.m., East Beltway location
- June 4, 6 p.m., Carmel Beltway location
- June 5, 5 p.m., Greenwood Beltway location
- June 9, 7-8 a.m., 10-11 a.m. or 1-2 p.m., Petticrew Auditorium, Methodist Hospital
- June 9, 4:30 p.m., Eagle Highlands Beltway location

For more information about the study or the Exception to Informed Consent, call Misinski at 929-2051.



## **Methodist Emergency Medicine and Trauma Center to study new investigational blood solution**

*You are invited to learn more about an important  
new national research study involving critically  
injured trauma patients*

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The study has been approved by the U.S. Food and Drug Administration and the Institutional Review Board of Methodist Hospital. Diaspirin Cross-Linked Hemoglobin is a new investigational blood solution which will be given to randomly selected trauma patients with life threatening injuries who are in shock from blood loss.

### **Meetings**

Join members of the Emergency Medicine and Trauma Staff to learn more about this study and its impact on trauma care. Learn what you need to know about the new FDA regulations on Exception to Informed Consent (waived consent). The new waived consent may be used if you and your family members are not available to give consent and the medical team treating you determines that participation in this investigational study could improve your chances of survival.

**June 6 Petticrew Auditorium**

**7 – 8 AM**

**10 – 11 AM**

**1 – 2 PM**





**May 29, 1997**

**Contact: Ann Myers  
(317) 929-5929**

### **Methodist Trauma Center To Study New Investigational Blood Solution**

Indianapolis - Methodist Hospital is participating in a national research study of a new blood solution that could dramatically affect the way severely injured patients are treated in emergency departments.

Methodist's Emergency Medicine and Trauma Center is one of 40 trauma centers studying whether a new blood solution can prevent deaths and reduce complications for trauma patients in shock because of severe blood loss. These severely injured patients have an estimated mortality of 40% despite today's aggressive treatment.

The study, which has been approved by the U.S. Food and Drug Administration and the Methodist Hospital Institutional Review Board, involves the administration of normal saline or a purified hemoglobin solution called Diaspirin Cross-Linked Hemoglobin (DCLHb™). Baxter Healthcare Corp. of Deerfield, Ill. is the study sponsor.

The blood solution is prepared from blood donated by healthy volunteers. This donated blood has been tested and found negative for the viruses that cause hepatitis and AIDS. The hemoglobin (which carries the oxygen to the cells) is taken from the red blood cells to make the solution.

When trauma patients are in shock because of severe bleeding, the loss of blood can damage or shut down vital organs such as lung and kidneys. Dr. George Rodman, Jr., Director of Trauma Service at Methodist Hospital notes, "This is the first new therapy in years that may help reduce the mortality of these severely injured patients." DCLHb™ has been shown to increase blood pressure and may bring more oxygen to the vital organs.

Severely injured patients, 18 years and older, admitted to the Methodist Emergency Department with persistent, severe, hemorrhagic shock are eligible for this study. Patients will be randomly assigned to receive either normal saline or the DCLHb™ solution. DCLHb™ or saline must be started within four hours of the time of injury. The solution or saline will be given in addition to all standard trauma resuscitation fluids, blood, and surgical interventions.

-more-

DCLHb page 2

DCLHb™ will not be given to pregnant women or patients with severe brain injuries. It will not be given on ambulances or on the LifeLine helicopter. Since DCLHb™ is made from human blood, it will not be administered to patients if it is known that their religious beliefs forbid blood transfusions.

Methodist is hoping to enroll 20 patients over the next 18 months. Baxter, the study sponsor is attempting to enroll 850 patients from 40 trauma centers.

Because trauma patients who would qualify for this study are so severely injured, they may not be able to give their consent to participate in this study. The U.S. Food and Drug Administration has granted an "Exception to Informed Consent" for this study. They have carefully evaluated the data from multiple trials and feel the potential benefits outweigh the patient's risk of participating in the trial.

Possible side effects can include: a temporary change in some lab test results; a temporary and harmless yellowing of the skin; temporary red color of urine; nausea, back, abdominal and muscle pain, and elevation of blood pressure. These side effects are usually gone within 96 hours of receiving the solution.

As a result, patients may be enrolled in this study and receive DCLHb™ when informed consent is not possible from the patient, their legal representative, or their family member. The investigators at Methodist will make every attempt possible to obtain consent from patients, their legal representative, or family before DCLHb™ is given.

All patients, and their family members will be completely informed of their participation as soon as possible and given the opportunity to decline further participation in the study. A patient may withdraw or be withdrawn from the study at any time without influencing his or her medical care.

The Trauma Center is sponsoring community meetings at each of the Methodist Medical Plazas listed below. Staff from the Emergency Medicine and Trauma Center will address the study protocol and the FDA's new regulations for an **Exception to Informed Consent**.

**June 3, 6 p.m., Methodist Medical Plaza East, 9660 East Washington Street**  
**June 4, 6 p.m., Methodist Medical Plaza Carmel, 141 Pennsylvania Parkway**  
**June 5, 5 p.m., Methodist Medical Plaza Greenwood, 8830 South Meridian Street**  
**June 9, 4:30 p.m., Methodist Medical Plaza Eagle Highlands, 6850 Parkdale Place**

If you have comments, questions, or would like to receive more information about this study, please call 1-800-833-2457 or write Methodist Hospital, Trauma Service B229, I-65 at 21st Street PO Box 1367, Indianapolis, Indiana 46206-1367.





**FACTS ON: *Purified Human Hemoglobin Solution Study*  
Methodist Emergency Medicine and Trauma Center**

**Summary**

Methodist Hospital is participating in a national research study of a new blood solution that could save the lives of more patients whose injuries cause severe bleeding and shock. The study, which has been approved by the U.S. Food and Drug Administration and the Methodist Institutional Review Board, involves the Emergency Room use of a purified hemoglobin solution that could raise blood pressure and speed up the time it takes to get oxygen to the vital organs. Hemoglobin is the red part of the human blood cell that carries oxygen throughout the body.

- Developed by Baxter Healthcare Corp. of Deerfield, Ill.
- Possible side effects can include: a temporary change in some lab test results; a temporary and harmless yellowing of the skin; temporary red color of urine; nausea, back, abdominal and muscle pain, and elevation of blood pressure. These side effects are usually gone within 96 hours of receiving the solution.

**The Study**

- Forty trauma centers will study 850 patients. Methodist is the only Indiana hospital involved at this time in the study.
- Due to the speed required to administer emergency medical treatment, the FDA has waived the informed patient consent requirements.
- Patients may receive the solution without prior consent, but will also receive all standard medical treatment.
- Every attempt will be made to obtain consent from the patient, their family member, or legal representative before the hemoglobin solution is given.
- A detailed protocol synopsis is available by calling 1-800-833-2457.

**The Need**

When patients suffer severe bleeding from traumatic injuries - such as those that may be experienced in an auto accident - the loss of blood can cause hemorrhagic shock and deprive vital organs of blood flow and oxygen that they need to keep on working. A salt solution injected by paramedics can help raise the blood pressure, but cannot deliver the needed oxygen to the organs. In an Emergency Room where every second is crucial to a patient's survival, doctors and nurses must get the right type of blood into a patient as fast as possible.

**Potential Benefits of DCHLb**

- Could decrease the number of patients who die from traumatic injuries.
- Could save precious time in the Emergency Room by eliminating the need to type and cross-match a patient's blood.
- Could reduce complications caused by shock such as respiratory failure and renal failure.
- Could enable units of red blood cells that are due to expire in Blood Banks to be recycled into a hemoglobin solution.

**The Product**

- Name : DCHLb
- Trademark name: HemAssist
- It is a concentrated hemoglobin solution made from red blood cell units that have been donated by healthy volunteers.



**Maureen Misinski,**  
**RN, MS, NP, CCRN**  
*Trauma Program Coordinator*

1-65 at 21<sup>st</sup> Street  
P.O. Box 7195  
Indianapolis Indiana  
46207-7195

317-929-2051 office  
317-928-5449 pager



SATURDAY, MAY 31, 1997

**NATION**

## **MEGAN'S LAW DECEASED**



# Consent issue is key in blood-solution study

By **Bill Theobald**  
STAFF WRITER

Some severely injured people taken to Methodist Hospital this summer may be given an experimental blood solution that could save their lives.

But they might not have the chance to give something else — their permission.

Methodist is one of 40 trauma centers nationwide participating in a study of the blood solution. It also will serve as a test of new regulations allowing people to be research subjects without their permission.

The ethical Catch-22 facing federal regulators and others is this:

How do you perform necessary tests of possibly lifesaving breakthroughs in emergency medicine when many of the patients are so severely injured that they need immediate care before consent can be obtained?

See **BLOOD** Page 2

# BLOOD

Continued from Page 1

The answer, approved in November by the U.S. Food and Drug Administration along with the National Institutes of Health, is to make the public aware that such "exception to informed consent" testing is taking place and to solicit comment.

That's exactly what Methodist is doing, with a series of meetings that start next week.

And it's an approach that drew praise from one medical ethicist.

"It seems like they are showing a lot of diligence. They're being right out front," said Dr. Jeremy Sugarman, co-director of Duke University Medical Center's Program in Medical Ethics.

"Emergency research poses a unique set of challenges — on the one hand we want results, on the other hand we want to make sure the rights of patients are respect-

## Meetings on study

Methodist Hospital will sponsor community meetings on a study it is conducting of a blood solution. Some people could be included in the study without their consent. The meetings will be:

■ Tuesday, 6 p.m., Methodist Medical Plaza East, 9660 E. Washington St.

■ Wednesday, 6 p.m., Methodist Medical Plaza Carmel, 141 Pennsylvania Parkway.

■ Thursday, 5 p.m., Methodist Medical Plaza Greenwood, 8830 S. Meridian St.

■ June 9, 4:30 p.m., Methodist Medical Plaza Eagle Highlands, 6850 Parkdale Place.

The blood solution involved is called diaspirin cross-linked hemoglobin (DCLHb). It is being developed by Baxter Healthcare Corp. of Deerfield, Ill., under the trade name HemAssist.

The purified hemoglobin solution is made from the part of red blood cells that carries oxygen. Giving it to people who have lost a lot of blood. It is hoped, will raise their blood pressure and carry oxygen to vital organs.

The saline solution that normally is given in such cases raises blood pressure but doesn't transport oxygen; blood transfusions require blood typing, something the solution does not.

Only minor side effects have been found in previous tests of the blood solution. And one study found that more than a third of heart surgery patients avoided the need for human blood in the first full day after surgery by taking several units of the solution.

In its emergency application, the goal is to lower the 40 percent mortality rate of severely injured patients.

Maureen Misinski, trauma coordinator for Methodist and coordinator for the study, explained how it would be conducted locally:

Starting in July, patients 18

years and older who are admitted to the Methodist Emergency Department with severe shock will be deemed eligible for the study. No one who is pregnant or has a severe brain injury will be included.

Misinski said normal emergency medical procedures will be followed in the field and at the hospital. And the usual efforts will be made to obtain consent.

But even if consent cannot be obtained, some patients may be included in the study. They will be assigned randomly to receive either normal saline, as a control, or the blood solution.

For the test to be valid, the solution must be administered within four hours of an injury and within one hour of arrival at the emergency room.

Patients or family members will be told of their participation as soon as possible and can choose to withdraw. People who know in advance they don't want to participate should carry some identification indicating that and let family

members know.

Participating patients will be tested for 28 days. Results will be sent along to Baxter, which will include them in reports to the FDA.

Each hospital, including Methodist, will be seeking 20 participants for the study. That will take about 18 months, Misinski said.

Out of 22,000 trauma cases Methodist handles annually, about 1,000 are serious enough for the patient to be admitted to critical care units, she said.

She said she and others at the hospital recognize the concerns the study might raise, which is why they are trying to get the word out in advance.

"It's a good issue; I just don't have an easy answer for it," she said. "For what it's worth, I would take this (the blood solution) without even thinking about it."

For more information or to express your opinion, call (800) 833-2457 or write Methodist Hospital, Trauma Service, B229, I-65 at 21st St., P.O. Box 1367, Indianapolis, Ind. 46206-1367



# EDITORIALS

*"Let the people know the facts  
and the country will be saved."*

ABRAHAM LINCOLN

## Abuse in research

**I**nformed consent is an established prerequisite for medical experimentation. Without it, the best of intentions count for nothing.

Perhaps the most egregious example of non-consent was the federal government's syphilis testing program in which a number of black men were deliberately left untreated so that researchers could study the progress of the disease. The experiments took place in Alabama during the 1930s.

Last month, President Clinton offered a lone survivor and families of the deceased a long overdue apology.

Earlier this year, Clinton signed a presidential order directing that federal agencies post new research rules protecting the rights of test subjects. Checks and safeguards were mandated to prevent abuse.

**Methodist has taken reasonable precautions to protect patients when using an experimental blood product.**

That order came in reaction to a 1995 report on human radiation experiments by government-funded scientists in the early years of the Cold War.

A presidential commission had recommended that apologies and cash compensation go to the fam-

ilies of 19 people who were injected with plutonium without their knowledge.

Such cases rouse public indignation. They also raise questions about how widespread the use of unwitting guinea pigs may be.

That is why Methodist Hospital is wise to allay fears regarding a study it is conducting on an experimental blood product. Because of the nature of the experiment, it is possible some emergency room patients will be included without their consent.

Methodist is one of 40 trauma centers nationwide participating in the testing of a blood product that could save the lives of severely injured accident or assault victims. It is anticipated that some participants could be in shock or unconscious and identification of next of kin may be impossible.

The product is said to raise blood pressure and facilitate the flow of oxygen to the vital organs of patients who have lost a great deal of blood. No blood typing is needed. There are time constraints, however.

The solution must be given within four hours of injury and one hour of arrival at the hospital. Attempts will be made to get consent in every case. But when that is impossible and the patient is a logical candidate, the hospital will act on its own.

Methodist has publicized its participation in the experiment in advance, scheduled public meetings to detail what will be involved and carefully explained potential problems with consent. Given the circumstances under which testing must be done, the hospital has taken every reasonable precaution to protect patients and alert the public.

If all experiments and research involving human subjects were as conscientiously planned, there would be no basis for private litigation and no reason for government apologies or tax-funded compensation.



# Methodist Emergency Medicine and Trauma Center to study new investigational blood solution

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*You are invited to learn more about an important new national clinical research study involving critically injured trauma patients.*

.....

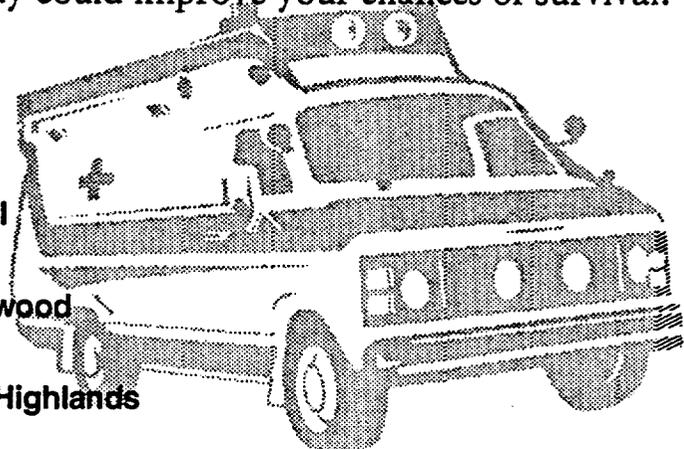
The study has been approved by the U.S. Food & Drug Administration and the Institutional Review Board of Methodist Hospital. Diaspirin Cross-Linked Hemoglobin is a new investigational blood solution which will be given to randomly selected trauma patients with life threatening injuries who are in shock from blood loss.

## Meetings

Join members of our Emergency Medicine and Trauma Staff to learn more about this study and its impact on trauma care. Learn what you need to know about the new FDA regulations on Exception to Informed Consent (waived consent). The new waived consent may be used if you and your family members are not available to give consent and the medical team treating you determines that participation in this investigational study could improve your chances of survival.

## Dates/Times/Places:

- **Methodist Medical Plaza East**  
*June 3 at 6 PM*
- **Methodist Medical Plaza Carmel**  
*June 4 at 6 PM*
- **Methodist Medical Plaza Greenwood**  
*June 5 at 5 PM*
- **Methodist Medical Plaza Eagle Highlands**  
*June 9 at 4:30 PM*





**B**

SUNDAY, JUNE 1, 1997

Online: [www.starnews.com](http://www.starnews.com)  
InfoLine: 624-4636

**METHODIST EMERGENCY MEDICINE AND TRAUMA CENTER TO STUDY  
INVESTIGATIONAL BLOOD SOLUTION IN TRAUMA PATIENTS**

Methodist Hospital is one of 40 Trauma Centers in the United States to participate in the evaluation of an investigational blood solution to be used in the treatment of critically injured patients 18 or older with severe blood loss and shock. Patients will receive all standard treatments, including blood, fluids and surgery, in addition to the investigational blood solution.

The study, which has been approved by the U.S. Food and Drug Administration and the Methodist Institutional Review Board, involves the administration of a purified human hemoglobin solution, Diaspirin Cross-Linked Hemoglobin (DCLHb(tm)). Baxter Healthcare Corporation is the study sponsor. Some temporary side effects of this solution may include harmless yellowing of the skin, temporary red color to urine, nausea, increase in blood pressure, and back, abdominal and muscle pain.

Because trauma patients who would qualify for this study are so severely injured, they may not be able to give their consent to participate in this study. The U.S. Food and Drug Administration has granted an "Exception to Informed Consent" (waived consent) for this study. This means that a critically injured patient may receive the investigational blood solution if the patient is in shock and there is no one who can give consent for the patient to be in this study. Patients or their families will be notified at the earliest opportunity of their inclusion in this research study. Patients or their families may decline further participation in this study.

The Trauma Service is sponsoring community meetings at each of the Methodist Medical Plazas listed below:

Methodist Medical Plaza East (9660 E. Washington St.).....	June 3 at 6 PM
Methodist Medical Plaza Carmel (151 Pennsylvania Pkwy.).....	June 4 at 6 PM
Methodist Medical Plaza Greenwood (8820-8830 S. Meridian St.).....	June 5 at 5 PM
Methodist Medical Plaza Eagle Highlands (6850 Parkdale Plc.).....	June 9 at 4:30 PM

If you have comments, questions, or would like to receive more information about this study, please call 1-800-833-2457 or write us at:

Methodist Hospital  
Trauma Service B 229  
1-65 at 21st Street. PO Box 1367  
Indianapolis, Indiana 46206-1367



A22 • THE INDIANAPOLIS STAR • SUNDAY, JUNE 8, 1997

**PARK****COL****METHODIST EMERGENCY MEDICINE AND TRAUMA CENTER TO STUDY  
INVESTIGATIONAL BLOOD SOLUTION IN TRAUMA PATIENTS**

Methodist Hospital is one of 40 Trauma Centers in the United States to participate in the evaluation of an investigational blood solution to be used in the treatment of critically injured patients 18 or older with severe blood loss and shock. Patients will receive all standard treatments, including blood, fluids and surgery, in addition to the investigational blood solution.

The study, which has been approved by the U.S. Food and Drug Administration and the Methodist Institutional Review Board, involves the administration of a purified human hemoglobin solution, Diaspirin Cross-Linked Hemoglobin (DCLHb(tm)). Baxter Healthcare Corporation is the study sponsor. Some temporary side effects of this solution may include harmless yellowing of the skin, temporary red color to urine, nausea, increase in blood pressure, and back, abdominal and muscle pain.

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If you have comments, questions, or would like to receive more information about this study, please call 1-800-833-2457 or write us at:

Methodist Hospital  
Trauma Service B 229  
I-65 at 21st Street, PO Box 1367  
Indianapolis, Indiana 46206-1367





## **TOWN MEETING AGENDA**

### **I. Traumatic Injury**

- A. Define trauma**
- B. Define severely injured patient**
- C. Why people die from trauma**
- D. Standard ER management of trauma patients**

### **II. Traumatic Hemorrhagic Shock**

- A. Define hemorrhagic shock**
- B. Impact of shock on vital organs**
- C. Current treatment of hemorrhagic shock**

### **III. Diaspirin Cross-Linked Hemoglobin Solution**

- A. What is it?**
- B. How safe is it?**
- C. Can Jehovah Witness patients take it?**
- D. What are side effects?**
- E. Who will be eligible?**
- F. How many patients?**
- G. How long will the patients be entered into the study?**

### **IV. Exception to Informed Consent**

- A. What is this and why was it necessary for this study?**
- B. What does the FDA require?**
- C. Review process for identifying trauma patients and contacting their family.**
- D. Call toll free 800 number to comment.**

### **V. Question & Answer Period**

**Trauma Staff Presenting is dependent on schedules.**

**Maureen Misinski, RN, MS at all sessions**

**Michael Olinger, MD**

**Charles Miraglia, MD**

**George Rodman, Jr., MD**





May 22, 1997

Dear Director and Nurse Manager, Emergency Department,

The purpose of this letter is to inform you of a clinical research study which will be implemented at Methodist Hospital in Indianapolis. Methodist is one of 40 Trauma Centers in the United States and Canada to participate in the evaluation of an investigational blood product to be used in the treatment of critically injured patients with severe blood loss and shock.

The study, which has been approved by the U.S. Food and Drug Administration and the Methodist Institutional Review Board, involves the administration of a purified human hemoglobin solution, Diaspirin Cross-Linked Hemoglobin (DCLHb). Baxter Healthcare Corporation is the study sponsor. The DCLHb solution has been shown to increase perfusion pressure and enhance oxygen delivery to the tissues and cells.

The study population will be trauma patients 18 years and older with persistent, severe, hemorrhagic shock despite aggressive therapies. This product has the greatest chance of improving survival and reducing complications when it is given immediately after the beginning of shock and bleeding. To enroll trauma patients in this study, we must start the DCLHb solution within four hours of the time of injury. DCLHb solution will be given in addition to all standard trauma resuscitation fluids, blood, and surgical interventions.

Because trauma patients who would qualify for this study are so severely injured, they may not be able to give their consent to participate in this study. The U.S. Food and Drug Administration has granted an "Exception to Informed Consent" for this study. They have carefully evaluated the animal and human trials and determined that the potential benefits greatly outweigh the risks of participating in the trial. As a result, patients may be enrolled in this study and receive DCLHb when informed consent is not possible. Under the new FDA regulations for granting an "Exception to Informed Consent", we must provide public notice about the study to potential patients.

We will make every attempt to obtain consent from patients, their legal representatives, or family before DCLHb is given. All patients, and their family members will be completely informed of their participation as soon as possible and given the opportunity to decline further participation in the study. We are hoping to enroll 20 patients over the next 18 months.

Enclosed is a protocol synopsis for your review. If you or your staff have any questions or concerns about this research study, please call 1-800-833-2457.

Thank you for your ongoing support of our Trauma program.

Sincerely,

George Rodman, Jr. MD FACS  
Director of Trauma Service, Principal Investigator

Maureen Misinski, RN, MS  
CS Trauma Program Coordinator, Study Coordinator





June 2, 1997

Dear

The purpose of this letter is to inform you of a clinical research study which will be implemented at Methodist Hospital in Indianapolis. Methodist is one of 40 Trauma Centers in the United States to participate in the evaluation of an investigational blood solution to be used in the treatment of critically injured patients with severe blood loss and shock.

The study, which has been approved by the U.S. Food and Drug Administration and the Methodist Institutional Review Board, involves the administration of a purified human hemoglobin solution, Diaspirin Cross-Linked Hemoglobin (DCLHb™). Baxter Healthcare Corporation is the study sponsor. The DCLHb™ solution has been shown to increase blood pressure and enhance oxygen delivery to the tissues and cells.

The study population will be trauma patients 18 years and older with persistent, severe, hemorrhagic shock despite aggressive therapies. This product has the greatest chance of improving survival and reducing complications when it is given immediately after the beginning of shock and bleeding. To enroll trauma patients in this study, we must start the DCLHb™ solution within four hours of the time of injury. DCLHb™ solution will be given in addition to all standard trauma resuscitation fluids, blood, and surgical interventions.

Because trauma patients who would qualify for this study are so severely injured, they may not be able to give their consent to participate in this study. The U.S. Food and Drug Administration has granted an "Exception to Informed Consent" for this study. They have carefully evaluated extensive trials with the blood solution and determined that the potential benefits greatly outweigh the risks of participating in the trial. As a result, patients may be enrolled in this study and receive DCLHb™ when informed consent is not possible. We will make every attempt to obtain consent from patients, their legal representatives, or family before DCLHb is given. All patients, and their family members will be completely informed of their participation as soon as possible and given the opportunity to decline further participation in the study. We are hoping to enroll 20 patients over the next 18 months. The study will begin in July.

The Trauma Service of Methodist Hospital is sponsoring community meetings at each of our Medical Plazas during the first two weeks in June. People in the community may call in their comments, concerns, or questions using 1-800-833-2457. If you or your staff have any questions or concerns about this research study, please call Maureen Misinski, RN, MS at 317-929-2051 or pager 928-5449.

Thank you for your ongoing support of our Trauma program.

Sincerely,

George Rodman, Jr. MD FACS, Director of Trauma Service, Principal Investigator

Maureen Misinski, RN, MS, CS Trauma Program Coordinator, Study Coordinator

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107 East 21st Street  
P.O. Box 1367

Indianapolis, IN 46201-1367

BB-IND #6859-013

317-929-2051  
317-929-5449

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June 2, 1997

Dear

The purpose of this letter is to inform you of a clinical research study which will be implemented at Methodist Hospital in Indianapolis. Methodist is one of 40 Trauma Centers in the United States to participate in the evaluation of an investigational blood solution to be used in the treatment of critically injured patients with severe blood loss and shock.

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Under the new FDA regulations for granting an "Exception to Informed Consent", Methodist is providing public notice about the study to potential patients. Our external communications plan includes press releases, town meetings, meetings with officials, and letters to officials, payers, and hospitals statewide.



Enclosed is a protocol synopsis and the FDA regulations regarding Exception to Informed Consent . If you or your staff have any questions or concerns about this research study, please call Maureen Misinski, RN, MS at 317-929-2051 or pager 928-5449. We are available to meet with you and your staff to discuss this study.

Thank you for your ongoing support of our Trauma program.

Sincerely,

A handwritten signature in black ink, appearing to read 'George Rodman, Jr.', written in a cursive style.

George Rodman, Jr. MD FACS, Director of Trauma Service, Principal Investigator

A handwritten signature in black ink, appearing to read 'Maureen Misinski', written in a cursive style.

Maureen Misinski, RN, MS, CS Trauma Program Coordinator, Study Coordinator



young children might be carried out). The Commission did not recognize the right of a needy person to gain access to a research protocol. In choosing among sites for a clinical investigation, for example, it is usual to select those in which the skills of investigators and availability of subjects appear to predict an ability to carry out the investigation successfully. Similarly, it is reasonable to consider, in deciding where or in whom to conduct an investigation, the ability of subjects to consent (or have consent given for them). Widely accepted ethical principles indicate that a decision to participate or not to participate in an investigation should, if at all possible, be made by a competent subject who should (as stated in the Nuremberg Code) be free of all force, fraud, fear, or coercion. An exception from the requirement for informed consent should be rare and narrow, confined to cases where consenting subjects are not reasonably available. In addition, participation in the research must hold out the prospect of direct benefit to the subjects and the investigation must be one that is capable of providing useful scientific/medical information.

If serving the interests of the subjects were considered sufficient alone, that would imply that potential subjects have a right to participate in the trial, an inappropriate consideration for an investigational use and unrealistic, because studies cannot in fact be carried out at all potential sites and in all patients.

The agency thus agrees with the comment that it is necessary for there to be value to the subject from participating in the research; but, given the general principle of obtaining informed consent where possible, does not think that such potential benefit is sufficient justification to include nonconsenting patients when it is reasonably possible to conduct the clinical investigation in subjects who can consent.

Therefore, if scientifically sound research can be practicably carried out using only consenting subjects (directly, or in most cases for the research contemplated in the rule, with legally authorized representatives), then the agency thinks it should be carried out without involving nonconsenting subjects. By practicable, the agency means, for example, (1) That recruitment of consenting subjects does not bias the science and the science is no less rigorous as a result of restricting it to consenting subjects; or (2) that the research is not unduly delayed by restricting it to consenting subjects.

#### 6. Section 50.24(a)(5)(i)-(a)(5)(iii)--Community Consultation and Public Disclosure

The greatest number of comments were received on Sec. 50.24(a)(5)(i) through (a)(5)(iii), which have been renumbered Sec. 50.24(a)(7)(i) through (a)(7)(iii) in this final rule in order to have a more logical presentation of information. To assist readers, these sections will be referred to as Sec. 50.24(a)(7)(i) through (iii) in the discussion that follows. While most comments supported the requirement for community consultation and public disclosure, many requested clarification, offered suggestions, or concluded that fulfilling these requirements would be impossible. Other comments questioned whose responsibility it would be to disclose--the clinical investigator, sponsor, or IRB. These comments are discussed in more detail below.

60. A number of comments suggested alternatives to the requirement for Sec. 50.24(a)(7)(i) for consultation with representatives of the communities from which the subjects will be drawn. These included limiting this provision to only those diseases for which a patient advocacy organization exists; relying on the existing IRB mechanism that already requires inclusion of an individual not otherwise affiliated with the institution; requiring that IRB's have a community member or an ad hoc community consultant who is intimately involved with the projected research population; permitting an IRB to determine that balanced community consultation is not

feasible and documenting and reporting this determination to the sponsor and to FDA; increasing public participation in the IRB process by specifying acceptable kinds of individuals (e.g., clergy, local commissioners, police, paramedics) who should be added to the IRB (limited to two); having the IRB membership include individuals from the community groups from which subjects would come and ensuring that the preferences of those members were followed; establishing a standing community advisory board that would reflect the diverse values and beliefs of the community. This board could serve several IRB's within the same community. Another comment stressed that the IRB must take into account the diverse religious and community beliefs and attitudes about treatment of the dying and of research.

None of the suggested alternatives to Sec. 50.24(a)(7)(i) would by themselves provide the protections of broad community consultation of this section. While an IRB may appropriately decide to supplement its members with consultants from the community, broader consultation with the community is needed for this type of research. The agency expects the IRB to provide an opportunity for the community from which research subjects may be drawn to understand the proposed clinical investigation and its risks and benefits and to discuss the investigation. The IRB should consider this community discussion in reviewing the investigation. Based on this community consultation, the IRB may decide, among other things, that it is appropriate to attempt to exclude certain groups from participation in the investigation; or that wider community consultation and discussion is needed. As described in the preamble to the proposed rule (60 FR 49086, September 21, 1995), IRB's should consider, for example, having a public meeting in the community to discuss the protocol; establishing a separate panel of members of the community from which the subjects will be drawn; enhancing the membership of the IRB by adding members who are not affiliated with the institution and are representative of the community; or developing other mechanisms to ensure community involvement and input into the IRB's decisionmaking process. It is likely that multiple methods may be needed in order to provide the supplemental information that the IRB will need from the community to review this research.

61. Another comment noted that tribal approval and not just consultation should be required and suggested that for American Indian/Alaska Native tribal governments, the regulation require approval by the tribal government for all research done within its jurisdiction. This comment suggested that the regulation permit a recognized government of the political community to disapprove research.

This regulation does not restrict or have an impact on any existing authority of tribal governments to review and approve or disapprove research that would otherwise be conducted on persons residing in tribal jurisdictional boundaries. If existing tribal authorities require tribal government approval of such research before it proceeds, then the tribal governments continue to have that authority. Thus, the agency thinks that adopting this suggestion is unnecessary.

62. Comments opposed to the community consultation required in Sec. 50.24(a)(7)(i) suggested that the current requirement for a community representative on the IRB (56.107(a)) was adequate; that this would be burdensome for noncommercially sponsored studies; that it was an insurmountable goal and that there is no guarantee that an IRB could reach all impacted individuals. Other comments suggested that only a central agency such as FDA or the Public Health Service should decide because the clinical investigator will bias the outreach meetings to a disinterested community that would be unable to make knowledgeable decisions, and the community will be biased because the research would bring funding support to the community,

and because it is difficult to define the community, especially for those institutions that receive patients from a large region or State. A number of comments suggested that community consultation could lead to IRB liability on the basis of failure to solicit adequate community participation in the decision process. Other comments noted that disclosure to the community does not substitute for consent and that unless one included information about the subject's right to refuse and how to exercise that right, community consultation would be inadequate.

As discussed previously, the agency does not think that the current IRB membership requirements adequately substitute for the community consultation called for in this rule. The agency thinks that community consultation provides a very important protection for research subjects and, therefore, every effort should be made by the IRB to involve, and consult with, the community from which research subjects may be drawn.

63. Other comments stated that without clear definition of terms, the vagueness of the requirement would lead to inadequate consultation and disclosure. Another comment noted that if minority or lower income populations were unlikely to agree to the research and they represented a large proportion of the potential research population, then the conduct of the research would violate the principle of justice because these populations would not share in its benefits or burdens.

The agency thinks that IRB's will ensure, through their review and oversight activities, adequate consultation and disclosure. It is impossible, without conscription, to ensure that each subpopulation shares both the benefits or burdens of all research. Achieving the principle of justice is a goal that must be balanced by other principles. In the case of a population that is unwilling to agree to participation in a research activity, honoring this population's unwillingness is, in effect, permitting the community to express its views.

64. A number of comments requested clarification of this requirement. These comments asked how the consultation should take place (newspaper, institutional newsletter, advertisement, local radio stations, meeting); who in the community needs to be informed and who may be legitimate representatives of the community; what the IRB does with the community response (e.g., can a community veto research, what if a small or a large number oppose the research, what is the sponsor or IRB's responsibility to respond to questions or requested changes in the research); how is an IRB to assess the effectiveness of the consultation (e.g., if there is a poor turnout at an adequately publicized meeting, is the IRB obliged to do more)? Another comment requested clarification of what the public representatives and representatives of the population at risk would be asked to do. One comment urged the agency to refrain from providing precise definitions for the various terms in Sec. 50.24(a)(7)(i) through (a)(7)(iii) in order to permit IRB's adequate flexibility in making judgments.

Community consultation is likely to be multifaceted and to use a number of the mechanisms suggested by the comments. As described earlier, the IRB needs to provide an opportunity for broad community discussion. If, for example, there is poor turn-out at a meeting to discuss the research, an IRB may consider targeting specific community representatives for inclusion in an additional meeting, or it may decide that the research was not found by the community to be objectionable. The IRB is responsible for listening and considering the community's support, concerns, etc., and then ultimately deciding whether the investigation should be modified, approved, or disapproved. The community is expected to provide input to the IRB on its support for or concerns about the research activity.

65. A number of comments requested clarification on who is responsible for the community consultation and disclosure requirements contained in Sec. 50.24(a)(7)(i) through (a)(7)(iii). Most comments suggested that the IRB should be responsible for reviewing and approving the content and method of consultation and disclosure; the sponsor should be responsible for developing the plan for consultation with the community and for disclosure and provide this information to the IRB to review for adequacy.

Although a sponsor may provide to an IRB model information for use in consultation with the community and for disclosure, just as it may now provide a model consent form for a clinical investigation, it is the responsibility of the IRB to ensure the adequacy of the community consultation and disclosure requirements contained in Sec. 50.24(a)(7)(i) and (a)(7)(ii).

66. Another comment recommended that the sponsor and clinical investigator should pay for the costs associated with the disclosure requirements.

The agency does not dictate the entity responsible for the costs related to research. However, the agency anticipates that the sponsor would normally incur the costs associated with disclosure to and consultation with the community.

67. Several comments on Sec. 50.24(a)(7)(ii) suggested that for multicenter trials, disclosure be required once for each metropolitan area and that the disclosure be made by the sponsor or a designated institution in a notice that would list all institutions, investigators, and IRB contacts.

The agency would not object to such centralized disclosure if all of the responsible IRB's agreed that this is appropriate and acceptable.

68. Another comment suggested that instead of requiring disclosure prior to the commencement of the study, disclosure occur at periodic time intervals (e.g., every 2 years) and include a public notice of general issues, specific projects, results of the research, and permit public input.

It is the responsibility of the IRB to consider how to maintain the flow of information to the community. In addition to requiring disclosure to the community prior to the initiation of the clinical investigation, the IRB may determine that it is appropriate to require further disclosure at periodic intervals of time.

69. Another comment requested that the regulation specifically ban "general disinformation campaigns" by sponsors performing the research.

The agency thinks that such a ban is unnecessary and that IRB involvement in the disclosure process helps to eliminate the possibility that biased or misleading information will be disseminated. The information disseminated will be reviewed by the IRB to ensure its adequacy and balance.

70. A number of comments were opposed to the requirements for disclosure contained in Sec. 50.24(a)(7)(ii). The comments suggested that they would take an exhaustive amount of time; could prevent valuable research because the investigator and institution could be targets of a poorly informed community; the investigator may not be the best individual to discuss the study; they could cause persons to not seek care; they would be burdensome for noncommercially sponsored studies; for parties with an interest in the research, a requirement for disclosure could lead to either a dishonest or incomplete disclosure of information; the regulation requires disclosure of less information than that which would be given to a research subject; that it is essential to include information about financial and economic incentives for the research; and that it is essential to permit public participation in the disclosure sessions.

As discussed previously, it is the IRB's responsibility to determine the information to be disclosed. As described in the preamble to the proposed rule, the IRB should consider how best to publicly disclose, prior to the commencement of the clinical investigation, sufficient information to describe the investigation's risks and benefits, e.g., relevant information from the investigator's brochure, the informed consent document, and investigational protocol. Initial disclosure of information will occur during the community consultation process. Disclosure of this information to the community will inform individuals within the community about the clinical investigation and permit them to raise concerns and objections.

71. Another comment suggested that the release of confidential information required by this section could serve as a disincentive for sponsors to conduct the research and that it would create a precedent that could affect companies not otherwise affected by the regulation.

The agency disagrees with this comment. While it is true that much information relating to clinical investigations is normally treated as confidential by sponsors, the agency believes that when a sponsor chooses to invoke the exception from informed consent contained in this rule that it is essential that reasonable disclosure occur to the community. The agency believes that the benefit to a sponsor of invoking the rule will outweigh concerns that a sponsor will have about disclosing information about the investigation. Because this disclosure is made only when the exception from informed consent is invoked, it will not create any precedent for companies not invoking the exception.

The agency notes that sponsors release research information to investigators and IRB's (for example, through the protocol and investigators brochure) and to potential subjects in the research through the informed consent process and informed consent form; this rule states that the same information should be released to the community so it can be informed as it considers the research.

FDA believes that American Indian and Alaska Native Tribal governments and communities currently require both presentation of the research protocol and reporting results to the community before they permit any research to occur on their reservation. Recent Phase 2 and Phase 3 trials of several vaccines (e.g., Haemophilus B, Hepatitis A, and rotavirus vaccines) have been done on reservations under those rules by the pharmaceutical companies sponsoring the research. Under this rule, no company is required to release additional information to a community if it does not want to have a waiver of consent for its emergency research.

72. One of these comments stated that information is a property right and to require that it be surrendered without compensation may violate the Fifth Amendment of the Constitution.

The agency disagrees with this comment. The Fifth Amendment requires that no private property be taken for a public purpose without just compensation. (U.S. Constitution, Amendment V.) One factor used to determine whether there has been a taking is whether the action interferes with the reasonable investment backed expectations of the owner of the alleged property right. (Kaiser Aetna v. United States, 444 U.S. 164, 175 (1979).) Where a voluntary submitter of information is aware of the conditions under which the information must be disclosed, the submitter gains an economic advantage related to the submission (such as registration), and the disclosure is rationally related to a legitimate government interest, there is no taking. (Ruckelshaus v. Monsanto Co., 467 U.S. 986, 1007-8 (1984).) Under this rule, the disclosure is directly related to protecting the individual members of a community that may be involved in the clinical investigation without informed consent by providing the community with advance notice of the nature of the investigation and the possibility that they may be involved in

the clinical investigation without their informed consent. Furthermore, the regulation provides a mechanism under which the sponsor may perform the clinical investigations and sets the conditions under which the disclosure will occur. Therefore, the regulation serves as advance notice that prevents a sponsor from having any reasonable investment-backed expectation concerning the information and, thus, there is no unconstitutional taking.

73. A number of comments raised questions about Sec. 50.24(a)(7)(ii) including: what criteria would be used to determine that disclosure was adequate; when is the disclosed information to be provided to FDA; what is meant by "sufficient" and "relevant"; whether it is sufficient prior to the study to simply post a notice on the bulletin board; who determines the adequacy of the disclosure; whether this places an obligation to "disclose" or to "disseminate" information to the community; what this disclosure is supposed to accomplish. Clarification was requested as to the method and scope of disclosure.

It is the responsibility of the IRB to determine the "sufficiency" of the information to be disclosed. The agency advises that this information could include, but may not necessarily be limited to, the information that is found in the informed consent document, the investigator's brochure, and the research protocol. The obligation to disclose information includes an obligation to disseminate information to the community. The purposes of disclosure are to provide community confidence in the role of the IRB and in its decisionmaking capability, to permit the community to express its concerns and possible objections to the research, and to inform the community so that it is aware that the research is to be conducted involving individuals from the community.

74. Another comment suggested that FDA and DHHS should provide IRB's with copies of disclosure forms.

The agency disagrees. It is the IRB's responsibility to determine the method for disclosure and information to be disclosed. A "form" would stifle IRB creativity and flexibility.

75. Comments on Sec. 50.24(a)(7)(iii) suggested that the regulation specifically include the requirement that the underlying data be disclosed following the end of the study; another suggested that product approval decisions should be based on compliance with this requirement as well as the timeliness of disclosure.

The agency does not think that these comments require a change in the regulation. The agency thinks that it is necessary to provide comprehensive summary data from the completed trial to the research community in order to permit other researchers to assess the results of the clinical investigation. The agency thinks that there must be a scientific need to conduct clinical investigations involving subjects who are unable to consent; if previous investigations have already provided the scientific answer, this should be shared broadly with the research community. Sufficient information may be contained in a scientific publication of the results of the completed investigation; in other instances, it may need to be supplemented by additional information. The agency has modified Sec. 50.24(a)(7)(iii) to clarify that the information to be disclosed is to include the demographic characteristics (age, gender, and race) of the research population.

In response to the suggestion that product approval decisions should be based on compliance with this requirement, the agency notes that it has a variety of compliance procedures that it may use to enforce this disclosure requirement.

76. Comments opposed to this disclosure requirement suggested that it would jeopardize the ability to publish the results of the research in peer review journals; it would foster unscientific

conclusions without peer review; an investigator cannot control the peer review process to ensure publication; it could negatively influence future trial recruitment and force a sponsor to disclose proprietary information. Several comments suggested that in multicenter studies, one institution may get a negative result, while another may get a positive result; thus, disclosure could be misleading. Comments suggested that updating the disclosure could be burdensome and that the disclosure itself could be considered dissemination of off-label use information and advertising. Another comment questioned the need for such disclosure because the community would have no opportunity to modify the research; another commented that the disclosure would be so delayed and the community to which the disclosure would occur has such insufficient knowledge to understand the disclosure, that the disclosure would be meaningless.

Some comments requested that the agency define what and how disclosure is to be accomplished; what is "sufficient" and what would constitute the "scientific community." One comment questioned whether the information that would be disclosed to the community and researchers would differ.

The comments opposed to this disclosure requirement illustrate a need for the agency to clarify what is intended by this section. For a multicenter investigation, the agency anticipates that the sponsor and/or lead investigators will be responsible for analyzing the results of the overall investigation, including the demographic characteristics of the research population, and that these results will be published (or reported in the lay press) within a reasonable period of time following completion of the investigation. Publication in a scientific journal or reports of the results by lay press, that would be supplemented upon request by comprehensive summary data, will enable the research community, e.g., researchers not connected to the clinical investigation, to learn of the research's results. Following publication, the IRB will be responsible for determining appropriate mechanisms for providing this information, possibly supplemented by a lay description, to the community from which research subjects were drawn. The usual rules of marketing and promotion apply to the disclosure of this information. The agency notes that it is common for the results of research to be reported in the lay press and published in peer reviewed journals.

77. One comment noted that the comment in the preamble that there would be a need for fewer subjects if disclosure took place did not recognize the possible need for replication of the research--a sound scientific principle.

In the preamble to the proposed rule, the agency stated that: "[b]y broadly sharing the results of the research with the scientific community, there may be less need to replicate the research; therefore, fewer subjects may be needed to obtain the same level of scientific knowledge and to advance emergency medicine." The agency recognizes that there is frequently a need to replicate research in order to verify its findings. The agency thinks, however, that broadly sharing both positive and negative results of research with the scientific community may reduce or eliminate unnecessary duplication of research that has been conducted and verified by others.

#### **7. Section 50.24(a)(5)(iv)--Data Monitoring Committees**

A number of comments on proposed Sec. 50.24(a)(5)(iv), which has been renumbered Sec. 50.24(a)(7)(iv) in this final rule, supported the requirement for the establishment of an independent data monitoring committee. These comments also requested clarification of the requirement and offered various suggestions. A discussion of these comments and the agency's response follows.

**3. Section 50.24 is added to subpart B to read as follows:**

**Sec. 50.24 Exception from informed consent requirements for emergency research.**

**(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:**

**(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.**

**(2) Obtaining informed consent is not feasible because:**

**(i) The subjects will not be able to give their informed consent as a result of their medical condition;**

**(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and**

**(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.**

**(3) Participation in the research holds out the prospect of direct benefit to the subjects because:**

**(i) Subjects are facing a life-threatening situation that necessitates intervention;**

**(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and**

**(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.**

**(4) The clinical investigation could not practicably be carried out without the waiver.**

**(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.**

**(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.**

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with Sec. 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Sec. 312.30 or 312.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

#### **PART 56--INSTITUTIONAL REVIEW BOARDS**

4. The authority citation for 21 CFR part 56 continues to read as follows:

Authority: Secs. 201, 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 379e, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C 216, 241, 262, 263b-263n).

5. Section 56.109 is amended by revising paragraph (c), by redesignating paragraphs (d) and (e) as paragraphs (e) and (f), by adding two new sentences to the end of newly redesignated paragraph (e), and by adding new paragraphs (d) and (g) to read as follows:

Sec. 56.109 IRB review of research.

\* \* \* \* \*

(c) An IRB shall require documentation of informed consent in accordance with Sec. 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may, for some or all subjects, find that the requirements in Sec. 50.24 of this chapter for an exception from informed consent for emergency research are met.

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(e)\* \* \* For investigations involving an exception to informed consent under Sec. 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under Sec. 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.

\* \* \* \* \*





June 2, 1997

Melvin Carraway  
 Superintendent  
 Indiana State Police  
 100 North Senate Blvd.  
 Indianapolis, Indiana 46204

Dear Mel,

The purpose of this letter is to inform you of a clinical research study which will be implemented at Methodist Hospital in Indianapolis. Methodist is one of 40 Trauma Centers in the United States to participate in the evaluation of an investigational blood solution to be used in the treatment of critically injured patients with severe blood loss and shock.

The study, which has been approved by the U.S. Food and Drug Administration and the Methodist Institutional Review Board, involves the administration of a purified human hemoglobin solution, Diaspirin Cross-Linked Hemoglobin (DCLHb™). Baxter Healthcare Corporation is the study sponsor. The DCLHb™ solution has been shown to increase blood pressure and enhance oxygen delivery to the tissues and cells.

The study population will be trauma patients 18 years and older with persistent, severe, hemorrhagic shock despite aggressive therapies. This product has the greatest chance of improving survival and reducing complications when it is given immediately after the beginning of shock and bleeding. To enroll trauma patients in this study, we must start the DCLHb™ solution within four hours of the time of injury. DCLHb™ solution will be given in addition to all standard trauma resuscitation fluids, blood, and surgical interventions.

Because trauma patients who would qualify for this study are so severely injured, they may not be able to give their consent to participate in this study. The U.S. Food and Drug Administration has granted an "Exception to Informed Consent" for this study. They have carefully evaluated extensive trials with the blood solution and determined that the potential benefits greatly outweigh the risks of participating in the trial. As a result, patients may be enrolled in this study and receive DCLHb™ when informed consent is not possible. We will make every attempt to obtain consent from patients, their legal representatives, or family before DCLHb is given. All patients, and their family members will be completely informed of their participation as soon as possible and given the opportunity to decline further participation in the study. We are hoping to enroll 20 patients over the next 18 months. The study will begin in July.

The Trauma Service of Methodist Hospital is sponsoring community meetings at each of our Medical Plazas during the first two weeks in June. People in the community may call in their comments, concerns, or questions using 1-800-833-2457.



If you or your staff have any questions or concerns about this research study, please call Maureen Misinski, RN, MS at 317-929-2051 or pager 928-5449.

Thank you for your ongoing support of our Trauma program.

Sincerely,

George Rodman, Jr. MD FACS, Director of Trauma Service, Principal Investigator

Maureen Misinski, RN, MS, CS Trauma Program Coordinator, Study Coordinator



## Summary of Questions Asked for Local Radio Broadcast

Radio Station WIBC

June 4, 1997

WIBC asked:

1. What is DCLHb™?
2. How is it made?
3. How safe is it?
4. How will patients be informed of the study?
5. Who has the liability if an enrolled patient has an adverse outcome?
6. What is the benefit of this solution over what is presently being done for trauma patients?

This interview was broadcast the next morning. Multiple Methodist staff members commented on the interview during the day. They thought it went very well and gave the public the facts about the study. The interview was also broadcast the week of June 10, 1997.



**For Immediate Release**

**Contact: Lisa Wolfington  
Senior Media Specialist  
Washington Hospital Center  
202-877-7072**

## **LOCAL HOSPITAL FIRST TO USE BLOOD SUBSTITUTE**

### **New Blood Product May Save More Lives**

**Washington, DC, January 31, 1997 – A new blood substitute product that is expected to revolutionize traditional trauma care and save more lives will be used for trauma patients at the Washington Hospital Center beginning in February 1997. The blood product is called Diaspirin Cross-Linked Hemoglobin (DCLHb) and has been in development for decades. The Hospital Center is the first hospital in the Washington, DC metropolitan area authorized by the FDA to use the product for a one-year clinical trial. It is one of the first hospitals in the country to be given permission to use the product without the consent of patients who have life-threatening trauma injuries.**

**The blood substitute, which is made from human blood, is sterilized and pasteurized like milk and can be frozen for a one-year period. Even when thawed, it lasts 21 days which is seven days longer than traditional fresh blood taken from donors. Most importantly, it does not require a cross match and can be used on anyone. The product is prepared from units of human red blood cells from volunteer donors who have been tested and found to be negative for the viruses that cause hepatitis and AIDS.**

**-1-**

"This breakthrough is the greatest thing to happen to patients since blood transfusions began," says Duncan Harviel, M.D., trauma surgeon at the Washington Hospital Center and the local investigation site of the clinical trial. "This blood product will eliminate many of the risks of allergic reactions. It is a product that will be found in the pharmacy. It will be the first ever universally available safe blood product."

Beginning February 1, 1997, the Washington Hospital Center will start using the blood substitute on severely injured trauma patients who have only a 60 percent chance of survival. "It will be given without consent only to patients suffering from extreme injuries," says Dr. Harviel. "We hope this product will give patients a greater chance of survival and that is why this clinical trial is being conducted here. We are thrilled with the honor to be one of the first hospitals in the country to have the opportunity to use this product."

Patients eligible for this study are suffering from a catastrophic traumatic event and are often not able to give consent due to their medical condition. Contacting a family member is often not possible because of the severity of the injuries and the need to act immediately to save the patient's life.

*Washington Hospital Center is a 907-bed tertiary, acute care facility located in Washington, DC. The largest non-profit hospital in the city, it offers a nationally ranked cardiac care program; the most advanced adult burn facility in the area; MedSTAR, one of the nation's top trauma centers; a comprehensive Cancer Institute and a full range of women's services.*

# # #



**For Immediate Release**

**Contact: Lisa Wolfington  
Senior Media Specialist  
202-877-7072**

## **LOCAL HOSPITAL FIRST TO USE BLOOD SUBSTITUTE**

### **Blood Product May Save More Lives**

**Washington, D.C., March 20, 1997 -- A blood substitute product that is expected to revolutionize traditional trauma care and save more lives will be used for trauma patients at the Washington Hospital Center beginning in March. The blood product is called Diaspirin Cross-Linked Hemoglobin (DCLHb) and has been in development for decades. The Hospital Center, which participated in safety trials on the blood substitute in 1995, is the first hospital in the Washington, D.C. metropolitan region authorized by the Food and Drug Administration to use the product for a one-year clinical efficacy trial. Washington Hospital Center is also one of the first hospitals in the country to be given permission to use the product without the consent of patients who have life-threatening trauma injuries. This study will comply fully with the FDA's regulations regarding exceptions from informed consent.**

**The blood substitute, which is made from human blood, is sterilized and pasteurized like milk and can be frozen for a one-year period. Even when thawed, it lasts 21 days which is seven days longer than traditional fresh blood taken from donors. Most importantly, it does not require a cross-match and can be used on anyone. The product is prepared from units of human red blood cells from volunteer donors who have been tested and found to be negative for the viruses that cause hepatitis and AIDS.**

"This breakthrough is one of the greatest things to happen to patients since blood transfusions began," says Duncan Harviel, M.D., trauma surgeon and principal investigator for the clinical trial locally. "This blood product will reduce many of the risks of allergic reactions. In addition, it can be given to any patient regardless of blood type. This means replacement for blood loss will not be delayed."

Beginning in March, Washington Hospital Center will start using the blood substitute on critically injured trauma patients whose chances of survival are 60 percent or less. "It will be given without consent only to patients suffering from extreme injuries," says Dr. Harviel. "We hope this product will give patients a greater chance of survival and that is why this clinical trial is being conducted here."

The substitute may be more effective than regular blood because it raises blood pressure more quickly and uses less volume to achieve the beneficial results. Thirty five medical centers across the country are participating in the randomized study of 850 patients over a one-year period.

Patients eligible for this study are suffering from a catastrophic traumatic event and are often not able to give consent due to their medical condition. Contacting a family member is often impossible because of the severity of the injuries and the need to act immediately to save the patient's life.

*Washington Hospital Center is a 907-bed tertiary, acute care facility located in Washington, D.C. The largest non-profit hospital in the city, it offers a nationally-ranked cardiac care program; the most advanced adult burn facility in the area; MedSTAR, one of the nation's top trauma centers; a comprehensive Cancer Institute and a full range of women's services.*

# # #





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## Transcript

DATE March 20, 1997  
TIME 5:00-6:00 PM  
STATION WJLA-TV (ABC) Channel Seven  
LOCATION Washington  
PROGRAM News 7 at 5:00

Kathleen Matthews, co-anchor:

A new blood substitute is soon gonna change the way hospitals save lives.

Del Walters, co-anchor:

Let's check in right now, with Rea Blakey, with today's medical alert. Rea?

Rea Blakey reporting:

We don't often have the chance to use the term 'revolutionary', but it certainly does apply this evening. It's expected to actually be revolutionary and to revolutionize trauma treatment and it could one day save your life. It is a blood substitute called 'Diaspirin cross-linked hemoglobin.' Now the Food and Drug Administration has authorized Washington Hospital Center to use that product in life-threatening trauma injuries, even without the patient's consent.

If you knew precisely when your life might be hanging on by a thread, perhaps after a horrifying car crash, well, you'd probably put some blood aside beforehand. The problem is, we don't know. And when a major trauma occurs, there's no time to go searching for blood products. That's why trauma surgeons like J. Duncan Harviel are quite excited about a product called Diaspirin.

Dr. Duncan Harviel (Trauma Surgeon, Washington Hospital Center): Once the person gets here, we're in the golden hour of saving the person's life. And this product, we are very hopeful, we'll bridge that gap and allow us to save more lives.

Blakey: Diaspirin is a blood substitute made from human blood, sterilized, pasteurized, and frozen.

Harviel: Taking the cells out eliminates any need to cross-match this blood. This is universally available.

For a videocassette(TV) or audio cassette(radio) of this news segment contact your nearest VMS office.

Material supplied by Video Monitoring Services may only be used for internal review, analysis or research. Any publication, re-broadcast or public display for profit is forbidden.

You just hang it and give it. You don't care what blood type a person is that's receiving it.

Blakey: The Diaspirin blood product is not perfect. It can break down and irritate the kidneys, cause yellowing of the skin or inflame the pancreas. But even fresh human blood can cause these side effects. Diaspirin can be frozen for a full year. And once thawed for usage, it will last seven days longer than traditional fresh blood.

Harviel: This is a great advance in the usage of blood, 'cause utilizing human blood in the trauma situation is one of the things that's been shown to save lives. So now we have a product that will do the same thing, carry oxygen, flow to the tissues, act like blood, but doesn't have the down side of 'I've got to give you your blood type.'

Blakey: Now Washington Hospital Center is one of thirty-five medical centers across the country that's participating in the research to confirm how well the Diaspirin product works. Patients who are eligible for this study, will be those who are facing life-threatening catastrophic traumas, such as a major beltway accident. But obviously, something like this could come in great, great need for people who are desperate to have blood products immediately and a large amount of them.

Walters: Okay. And it's- you gotta admit, nowadays, it seems like almost there is a medical change or breakthrough. It's an exciting time to be covering this, right now.

Blakey: Absolutely.

Walters: Okay. Thanks a lot, Rea.

# # #



# WASHINGTON HOSPITAL CENTER

## COMMUNITY RELATIONS COUNCIL MEETING

THURSDAY, APRIL 24, 1997

5:30 PM

CANCER INSTITUTE AUDITORIUM

### AGENDA

I. *Call to Order*

II. *Tour of MedSTAR*

**Kristin Brandenburg**  
(Research Nurse  
Coordinator)

\*\*\*\*\* DINNER \*\*\*\*\*

III. *Clinical Trial of New Blood Substitute Product*

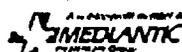
**Daniel Herr, M.D.**  
(Chairman of the Institutional Review  
Board for WHC, Medical Director  
of Surgical ICU)

**Max Koningsburg, M.D.**  
(Associate Professor of Emergency  
Medicine at the University of Illinois  
& Coordinating Investigator for all sites)

**Dennis Wang, M.D.**  
(Attending Surgeon, Trauma &  
Surgical IntensiveCare Unit)

A new blood substitute product that is expected to revolutionize traditional trauma care and save more lives will be used for trauma patients at the Washington Hospital Center beginning in March. The blood product is called Diaspirin Cross-Linked Hemoglobin (DCLHb) and has been in development for decades. The Hospital Center, which participated in safety trials on the blood substitute in 1995, is the first hospital in the Washington, D.C. metropolitan region authorized by the Food and Drug Administration to use the product for a one-year clinical efficacy trial. Washington Hospital Center is also one of the first hospitals in the country to be given permission to use the product without the consent of patients who have life-threatening trauma injuries.

110 IRVING STREET, NW  
WASHINGTON, DC 20010-2975



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# WASHINGTON HOSPITAL CENTER

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## *The Efficacy Trial of Diaspirin Cross - Linked Hemoglobin (DCLHb) in The Treatment of Severe Traumatic Hemorrhagic Shock.*

### **Washington Hospital Center: Public Disclosure**

Meeting with Community Relations Council, April 24, 1997

- 1) Dr. Daniel Herr, IRB Chairman Washington Hospital Center, discussed:
  - \* New FDA regulations
  - \* Waived trial consent explanation
  - \* IRB role within The Washington Hospital Center
  
- 2) Dr. Dennis Wang, Trauma Surgeon and Co Investigator of Trial, discussed:
  - \* Introduction and brief synopsis of the trial
  - \* Role of the Washington Hospital Center and trauma unit
  - \* Reason for community disclosure
  
- 3) Dr. Max Koningsburg, Emergency Department discussed,
  - \* Role of the Community Relations Council
  - \* His role in the trial as Coordinating Investigator for all sites
  - \* Experience with other sites, their IRB and their community disclosure plan
  - \* Role of Baxter, the media and the FDA in the trial
  - \* The history behind the trial and the endpoints of the

Questions were encouraged and examples of some of the questions were:

**Q. Why were other hospitals in the Washington D.C area not included in the trial especially Howard Hospital?**

**A.** All trauma centers in the Washington D.C area were invited to participate but most declined participation at this time. Some hospitals felt their trauma population did not support the criteria necessary for participation and others were waiting to see the reaction to Washington Hospital's participation.

110 IRVING STREET, NW  
WASHINGTON, DC 20010-2975

  
**MEDLANTIC**  
 BB-IND #6859-013

**Q. Is there consideration given to the population who may feel they are being used as guinea pigs in this trial?**

A. No patient is considered a guinea pig and those who have already participated in the trial at another site are grateful to be included in the trial.

**Q. What is our role as Community Relations Council?**

A. Your role is very important and will allow us access to members of the community who may wish to have further information regarding the trial. We are very interested in any feedback you may have.

The following was also discussed :

- a) The Community Council will have input with the media personnel for future press releases.
- b) The Council would select a key focus group who would continue participation with us throughout the duration of the trial.
- c) A small group would meet with the Principle Investigator, J Duncan Harviel, M.D. to discuss any other issues .

\* \* \* \*

On June 2, 1997, the Study Coordinator met with the Director of Community Relations, to discuss any feedback from the meeting. Feedback was generally positive. It was agreed that a few key members of The Council who were not present at the initial meeting would be given the opportunity to discuss the trial with Dr. Harviel at a later date.



WASHINGTON  
HOSPITAL  
CENTER

*The Efficacy Trial of Diaspirin Cross - Linked Hemoglobin (DCLHb) in  
The Treatment of Severe Traumatic Hemorrhagic Shock.*

**Washington Hospital Center: Public Disclosure**

**Media opportunities for discussion of DCLHb**

**April 16, 1997.**

Dr. Harviel (PI of the Trial) was interviewed on a local radio program, WTOP. He spoke for 3 minutes on the outline of the trial, the waiver of consent and community involvement.

**May 6, 1997:**

Dr. Harviel (PI of the trial) discussed the safety, efficacy, waived consent issue and endpoints of DCLHb. He stressed the community involvement in the project.

This was an 8 minute interview, placed in a health segment called, *HealthLine* and replayed for a total of 9 times during the weekend of May 9, 10, 11, 1997.

Attachment 27

Washington Times

5-26-97

# New industry's lifeblood holds promise for sick

## Area hospitals testing substitutes

By Samuel Goldreich  
THE WASHINGTON TIMES

Blood transfusions may soon be as easy as pouring a cup of instant coffee, if research at Georgetown University Medical Center proves successful.

"If we can make freeze-dried coffee, we can do it with something more important to help cancer patients stop their bleeding," said Dr. Gerald Sandler, director of Georgetown's blood bank.

Georgetown is one of 10 hospitals nationwide anticipating Food and Drug Administration clearance next month so they can begin testing whether frozen platelets — sticky disc-shaped components of blood — can carry on their vital clotting function after being thawed. That could help save the lives of cancer patients, who need reliable supplies of platelets be-

cause chemotherapy makes patients susceptible to uncontrolled bleeding.

The research at Georgetown is part of the nascent "blood substitute" industry, on which Wall Street is placing heavy bets in hopes of a multibillion-dollar payoff.

Scientists have searched for ways to manufacture blood since the 17th century, experimenting with everything from wine to milk. The quest took on new urgency during the 1980s with the onset of AIDS and concerns about the safety of donor-blood supplies.

Now, researchers are breaking blood down to its components, creating specialized products for different functions such as clotting and carrying oxygen.

Washington Hospital Center is a  
see BLOOD, page A9

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# BLOOD

From page A1

clinical trial site for Baxter Healthcare Corp. of Deerfield, Ill., which has developed HemAssist, an oxygen-carrying product developed from hemoglobin, a blood protein.

Baxter's blood substitute could prove a lifesaver for emergency room patients who risk bleeding to death if a hospital has depleted its inventory of real blood.

"This breakthrough is one of the greatest things to happen to patients since blood transfusions began," said Dr. Duncan Harviel, a Washington Hospital Center trauma surgeon and lead investigator for the local clinical trial. "This blood product will reduce many of the risks of allergic reactions. In addition, it can be given to

any patient regardless of blood type."

In Baltimore, University of Maryland Medical School researchers are administering hemoglobin-based blood substitutes to cats and rats in order to trace how defects in blood circulation can lead to strokes and heart attacks.

"The potential of these fluids is enormous," said Dr. Enrico Bucci, a biochemistry professor at the medical school. "In some ways, I'm sorry that these companies are involved only in the substitution of blood to carry oxygen."

The medical science behind blood substitutes is complex, but the motivation is simple. With 14 million units of donor blood transfused annually in the United States alone, analysts estimate that the market could reach \$8 billion a year.

One of the big winners could be Northfield Laboratories, a company that went public in 1994 but has never shown a profit in its 12-year history. Northfield has invested more than \$120 million in the development of PolyHeme, an oxygen-carrying product developed from hemoglobin.

The company already has had substantial emergency room success, said Richard DeWoskin, Northfield's chief executive officer.

"We transfused 10 units in 22 minutes this week to a patient with a gunshot wound and saved him from bleeding to death," he said.

Ten units is the equivalent of replacing a body's entire blood supply.

Northfield, which plans to begin building a manufacturing plant in the fall, wants to cut its costs enough to price PolyHeme com-

petitively with whole blood when it reaches the market, Mr. DeWoskin said.

Recently, scientists seemingly claim they can squeeze blood out of everything but stones. Researchers across the nation have been able to develop blood substitutes out of animal blood, bacteria, fluorocarbons and even genetically engineered tobacco plants.

But with all the hype, there are signs that some of the biggest pharmaceutical companies are losing faith in a financial return on blood substitutes. Last year, Pharmacia & UpJohn Inc. ended its synthetic-blood research project with Biopure Corp., and Eli Lilly & Co. ended its research agreement in March with Somatogen Inc., which is developing genetically engineered hemoglobin-based products.

p. 2 of 2



**Washington Hospital Center MedSTAR Unit to Test Drug:**  
*Blood product may save trauma victims*

The Washington Hospital Center's MedSTAR Unit has been selected to be among 35 trauma centers to evaluate a product for treating patients with severe blood loss many of which may die despite the best current medical therapy. Diaspirin Cross Linked Hemoglobin (DCLHb) developed by Baxter Healthcare will be used for critically injured trauma patients with severe blood loss. The U.S. Food and Drug Administration (FDA) has authorized this trial. Since many of these patients will be unable to consent to participate (due to their blood loss) the U.S. FDA has requested public disclosure. The purpose of this public notice is to give information about the trial and to address questions.

**Q.** What is DCLHb?

**A.** DCLHb is made from human red blood cells. The product is filtered and heated to reduce the risk of infectious viruses such as AIDS and Hepatitis. Blood typing is not required. DCLHb will be stored in the trauma center (MedSTAR unit) so that it is immediately available to the patient thus saving critical time.

**Q.** Why is this trial being done?

**A.** As many as 40% of severely injured patients with extreme blood loss may die despite early and intensive medical care. DCLHb may offer these patients a better chance of survival.

**Q.** Does DCLHb replace the need for blood transfusion?

**A.** DCLHb will be given in addition to any blood products needed. Patients will still receive all standard therapy including blood, fluid and surgery. DCLHb may reduce the number of transfusions required for the patient. Volunteer blood donations are still needed.

**Q.** What is an exception of informed consent and why it is necessary?

**A.** Because trauma patients are often so severely injured, they may not be able to give their consent to participate in a drug trial. The U.S. FDA has granted an exception to informed consent in these cases. Following careful review of DCLHb the U.S. FDA has determined that the potential benefits outweigh the risks of participation. Every attempt will be made to obtain consent from the patient, responsible family member or legal representative. Family members will be notified of patients participation as soon as possible.

Patients or their responsible family members may decline or discontinue participation at any time.

**Q.** What are the risks and side effects of DCLHb?

**A.** DCLHb has been evaluated for 4 years in patient studies and a few side effects have been noted. These side effects include temporary changes in lab results, yellowing of the skin (unrelated to liver damage), a red color in the urine (due to the red color of DCLHb), abdominal pain and a rise in blood pressure. An independent safety committee will monitor patient safety during the trial.

**Q.** Who will be eligible to participate?

**A.** Patients with low blood pressure and in shock from blood loss will be enrolled. A total of 850 patients nationwide will be enrolled. The trial has been approved by our (WHC) Institutional Review Board and cleared by the FDA.

**Q.** How do I obtain more information or where do I direct my questions?

**A.** You may contact Washington Hospital Center, Trauma Research Team at 110 Irving Street, NW, Suite 4B39; phone 202-877-6424 or by fax, 202-877-3173 or Medlantic Research Institute, Office of Research Programs, Barbara Howard, M.D., President, 108 Irving Street, NW, #242, Washington, DC, 20010; phone 202-877-6536 or by fax, 202-877-3209.



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WASHINGTON POST = Memo 6/26/97.



BETTER HEALTH FOR LIFE FROM LEHIGH VALLEY HOSPITAL AND HEALTH NETWORK

# Healthy You

MARCH/APRIL 1997

## Hospital Studies Blood Substitute That Could Save Lives of Trauma Victims

Lehigh Valley Hospital (LVH) has started two research studies to test a new blood substitute that could help save the lives of trauma patients and potentially ease the growing demand on community blood banks. LVH is one of only seven sites in the country to study the substitute's use in elective surgeries and one of only 30

sites for the trauma study.

The substance, an oxygen-carrying hemoglobin solution, is one of an exciting new group of blood substitutes that has the potential to affect millions of people.

The blood substitute carries oxygen through the bloodstream until the patient can be stabilized. It does not have to be typed and cross-matched as blood does, and is free of the risk of infection. It has proven to be non-toxic and involves few side effects.

LVH was chosen to take part in the study because of the large number of patients in its trauma center and the array of specialists to support research studies.

Call (610) 402-CARE for information on either blood substitute study.