



February 26, 1998

2107 '98 MAR -2 AIO :28

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 IRBs at University Hospital in Cincinnati, OH, and also includes a copy of the University of Illinois-Chicago's web site which is posted on the World Wide Web. The web site was developed by the University of Illinois-Chicago to fulfill public disclosure requirements under the applicable regulations.

The public disclosure/community consultation information from University Hospital includes a letter (Attachment 1) and notification of the study (Attachment 2) sent out to nearly 400 congregations, including Jewish, Orthodox, Catholic, Protestant, and Muslim congregations in Ohio and Northern Kentucky the week of August 4, 1997; an article that was published in the local newspaper, *The Cincinnati Enquirer*, on August 18, 1997, describing the study (Attachment 3); an advertisement that was published in the August 21-27, 1997 edition (Attachment 4) and August 28-September 3, 1997 edition (Attachment 5) of a local newspaper, *CityBeat*; a transcript of a television news broadcast that aired on August 18, 1997 on a local ABC affiliate station, WCPO-TV (Attachment 6); a copy of an advertisement that was published in the local newspaper, *The Cincinnati Enquirer*, on August 20, 24, 27 and 31, 1997 (Attachment 7); a copy of a press release that was posted on the *Beacon/Journal* Web Site (www.ohio.com) (Attachment 8); minutes from a June 6, 1997 MARCC (Metropolitan Area Religious Coalition of Cincinnati) Meeting (Attachment 9); an August 27, 1997 University Hospital press release describing the study (Attachment 10); and a transcript of a local radio program, WCIN, which aired on October 28, 1997, and featured trauma surgeons from the University Hospital (Attachment 11).

95S-0158

SUP 16

In summary, based on the information received from the clinical site, the investigator and IRB of University Hospital received community consultation by mailing study notifications to religious congregations (Attachment 2), publishing advertisements of the study in local newspapers (Attachments 4, 5, and 7), holding a meeting with area religious coalitions (Attachment 9), and broadcasting on a local television (Attachment 6) and radio (Attachment 11) station. In addition, the information sent to the various congregations (Attachments 1 and 2), the article and advertisements in the newspapers (Attachments 3,4,5, 7), the television broadcast (Attachment 6), the press release (Attachment 10) and the radio broadcast (Attachment 11) all provided a dedicated phone number and/or an address for community comments. A total of 65 telephone calls were received by the Trauma Research Office.

Additionally, we include in this submission a copy of the University of Illinois-Chicago web site related to the DCLHb Traumatic Hemorrhagic Shock Research (<http://dclhb.er.uic.edu>) (Attachment 12). The web site was developed by the University of Illinois-Chicago to fulfill public disclosure requirements under the applicable regulations.

The submission has been organized as follows:

- Attachment 1: Letter sent to religious congregations the week of August 4, 1997
- Attachment 2: Notification of the study sent to religious congregations the week of August 4, 1997
- Attachment 3: August 18, 1997 article in *The Cincinnati Enquirer*
- Attachment 4: August 21 -27, 1997 advertisement in *CityBeat*
- Attachment 5: August 28-September 3, 1997 advertisement in *CityBeat*
- Attachment 6: Transcript of August 18, 1997 television news broadcast
- Attachment 7: Advertisement published in *The Cincinnati Enquirer* on August 20,24, 27 and 31, 1997
- Attachment 8: Press release posted on *Beacon/Journal* Web Site
- Attachment 9: Minutes from June 6, 1997 MARCC Meeting
- Attachment 10: August 27, 1997 University Hospital press release
- Attachment 11: Transcript of October 28, 1997 radio program
- Attachment 12: DCLHb Traumatic Hemorrhagic Shock Research Web Site

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

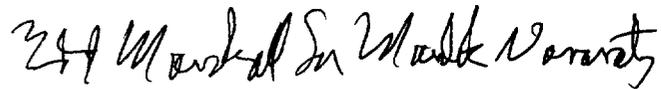
Dockets Management Branch (HFA-305)
February 26, 1998

IND # 6859
Page Three

This IND (BBIND #6859) is cross-referenced to Baxter's original BBIND #4426 and subsequent amendments.

If there are any questions concerning this submission, please contact me at (847)270-53 13.

Sincerely,

A handwritten signature in black ink that reads "Maulik Nanavaty". The signature is written in a cursive style with some loops and flourishes.

Maulik Nanavaty, Ph.D.
Director Regulatory Affairs
Hemoglobin Therapeutics Program

Attachment 1

1

University of Cincinnati
Medical Center



Kenneth Davis, Jr., MD, FACS
James M. Hurst, MD, FACS
Fred A. Luchette, MD, FACS
Jay A. Johannigman, MD, FACS
Richard D. Branson, RRT

college of Medicine
Department of Surgery

Division of Trauma/Critical Care
231 Bethesda Avenue
Phone: (513) 558-5661

UNIVERSITY OF CINCINNATI
PO BOX 670558
CINCINNATI OH 45267-0558

July 30, 1997

Dear Sir/Madam:

I am a Trauma Surgeon at the University of Cincinnati Medical Center. As you know, the hospital is a Level One Trauma Center. We are proposing to perform a study involving a new medication for injured patients. This study will be done giving the medicine without the patient's consent. The enclosure explains the drug and the protocol, and is asking the community for their input regarding the waiver of informed consent.

I recently met with Reverend Holmes and other members of MARCC. Reverend Holmes suggested that we ask each denomination to post this flier in an appropriate area for the members of the congregation to review,

If you should have any questions, please do not hesitate to contact our office at 558-3850. I thank you in advance for your assistance in informing your community about this proposed study,

Sincerely,

Fred A. Luchette, MD, FACS
University of Cincinnati Medical Center

FAL:jlr

Attachment 2

University Hospital
Study of a Blood Substitute For Injured Patients
With Severe Blood Loss

The University of Cincinnati and University Hospital have been asked to participate in the study of a new treatment for patients with massive blood loss following trauma (automobile accidents, falls, gunshot wounds, "etc."). The treatment, developed by Baxter Healthcare Inc., is a patented product which can serve as a blood substitute during emergency treatment. This treatment has been used in over 350 patients world wide.

The University of Cincinnati and University Hospital would like to make this treatment available to accident victims. Because accidents are never planned and family members are rarely available during the important early treatment period, we would like to offer the treatment to patients who cannot sign a consent for themselves. The patients who would receive the treatment will be critically ill and unable to sign a consent because of their life-threatening injuries. The treatment will not change the way the doctors treat patients, All patients will continue to receive blood and other intravenous fluids as required. The study drug will be in addition to the regular treatment.

The U.S. Food and Drug Administration (FDA) requires new drugs and treatments to be proven effective in human volunteers before the drug or treatment can be marketed. The FDA has recently ruled that under strict circumstances, unconscious patients whose lives are in danger (and no family members are present to give consent), may be given experimental treatment if there are not other treatments available which have a good chance of success. The patients who might receive the drug and their families will be notified at the earliest opportunity of their inclusion in the research study.

We believe injury victims with massive loss of blood meet all of the conditions set forth by the FDA. That is, these patients could be included in a study without informed consent, because they would be too sick to understand and sign. The FDA requires the University of Cincinnati and the University Hospital to inform the public of this research study and that patients would be enrolled in the study without informed consent. The FDA also requires that we receive public input before a decision is made to begin the research study.

We invite you to communicate with us on this subject. Please call the Research Office at 513-558-3850 or write us at the following address

University of Cincinnati
Department of Surgery
Trauma Research
PO Box 670558
Cincinnati, Ohio 45267-0558

Attachment 3

1

Public opinion will influence new blood's use

Artificial product called lifesaver

BY TIM BONFIELD

The Cincinnati Enquirer

Greater Cincinnati's leading trauma center wants to find out whether artificial blood really works.

But before researchers test it, they want to know whether the community supports the project, including the idea of using artificial blood on patients without their consent.

It will be the first time in Cincinnati history that public opinion will directly influence the launching of a clinical trial.

The new product may help save lives when people suffer massive injuries from car accidents, shootings or stab-

bing. But to find out how well artificial blood works, researchers at the University of Cincinnati and University Hospital need to try the product in real trauma victims. In many cases, the patient will be unconscious and there won't be time to find a

To comment

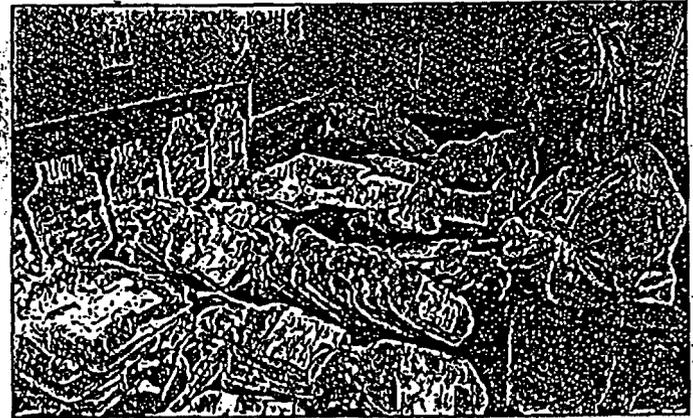
Those interested in registering an opinion about the artificial blood trial proposed to start this fall at University Hospital can write or call researchers at the University of Cincinnati, Dept. of Surgery, Trauma Research, 231 Bethesda Ave., Cincinnati OH 45267-0558; (513) 558-3850.

relative to sign a consent form.

Beginning Wednesday, advertisements are scheduled to appear to give notice and solicit public comment about artificial blood.

"We're trying to come up with an acceptable plan to inform the community about the study and to get their input," said Dr. Fred Luchette, a trauma surgeon and the lead researcher for the UC artificial blood study. "If the community feels we should proceed, the clinical trial would start this fall."

The experiment involves a type of artificial blood that



The Cincinnati Enquirer/Gary Lenders

Hoxworth Blood Center technician Vicky Johnston checks blood platelets before they are stored. Researchers want to test artificial blood here that does not require finding a person's blood type.

has been in development for several years — a product called HemAssist, made by Baxter HealthCare Corp. of Deerfield, Ill. If the public approves, UC would become one of nine trauma centers nationwide to test the product.

The Cincinnati study would involve about 30 patients for one year. The patients would be among the most severely injured who come to University Hospital's emergency department. The injuries will be so severe that only 50 percent of patients would normally be expected to survive, Dr. Luchette said. The hospital sees about 100 such patients a year.

HemAssist is not blood, but it is made from human blood. The product is a chemical solution containing large amounts of hemoglobin, the key oxygen-carrying protein normally found in red blood cells.

The main idea behind HemAssist is to save lives by saving time. Unlike regular blood, the product can be used in anybody without doing cross-match tests to check for blood type, which can take an hour.

Doctors also think the smaller particles in the artificial blood will be more effective than larger, whole red blood cells at preventing or-

(Please see BLOOD,
Page A5)

Blood: Public input will sway new blood's use

000-000004

CONTINUED FROM PAGE A1

gan damage in cases of traumatic shock.

In previous tests, more than 350 patients have received the artificial blood without experiencing any significant harmful side effects, Dr. Luchette said. This latest round of testing is less about safety than about measuring how well the product works.

The goal is to improve survival rates for severe trauma patients by 10 percent or more, Dr. Luchette said.

The unusually public process launching the study is Cincinnati's answer to new regulations from the U.S. Food and Drug Administration (FDA) that took effect in September.

In limited circumstances, the FDA will allow doctors to do experiments without patient consent if the patient is unconscious and his or her life is in immediate danger, there are no relatives around to ask for consent and there are no other established treatments that have a good chance of success.

In such situations, the FDA requires researchers to seek public comment and give public notice that their institution is involved in the experiment. Researchers also are required to seek after-the-fact notification and consent from patients or their families as soon as possible.

Once advertising begins, the public will have three weeks to send comments. The replies will not be treated as votes — there is no set number of positive or negative comments that will decide the question.

Instead, the comments will go to UC's Institutional Review Board, which must approve all medical experiments involving the university. Officials say the public comments will have a powerful influence on the board's decision.

"This is the first time investigators have been asked to go to the community. I think it's a great idea," Dr. Luchette said.

THE CINCINNATI ENQUIRER

About HemAssist

HemAssist is the trade name for Diaspirin Cross-Linked Hemoglobin, made by Baxter Health Care Corp. of Deerfield, Ill. HemAssist is a blood substitute made from human blood collected from blood banks after it has become too old for regular uses.

The product is a chemical solution containing large amounts of hemoglobin, the oxygen-carrying protein normally found in red blood cells. Doctors think the product will help save lives in several ways:

► Time would be saved by reducing the need for cross-matching blood tests, which can take up to an hour.

► Unlike whole blood, which cannot be stored longer than six weeks, artificial blood can be stockpiled for six months to a year. That makes it easier to use in emergency rooms, ambulances and disaster relief.

► The particles in artificial blood are smaller than whole blood cells. This may be important in treating traumatic shock, because blood vessels tend to constrict during shock. The smaller particles may help reduce organ damage caused by blood loss by moving farther along tiny blood vessels.

► Artificial blood might be safer. Although blood banks test supplies for AIDS, hepatitis and other diseases, a slight risk remains that a patient will get a contaminated transfusion. Artificial blood is treated to kill viruses, which cannot be done for whole blood.

Doctors say the product cannot duplicate all the benefits of whole blood transfusions. Even if the product proves successful, demand will continue for voluntary blood donations.

Attachment 4

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University Hospital Study of a Blood Substitute for Injured Patients with Severe Blood Loss

The University of Cincinnati and University Hospital have been asked to participate in the study of a new treatment for patients with massive blood loss following trauma (automobile accidents, falls, gunshot wounds etc.) The treatment developed by Baxter Healthcare Inc., is a patented product which can serve as a blood substitute during emergency treatment. This treatment has been used in over 350 patients world wide.

The University of Cincinnati and University Hospital would like to make this treatment available to accident victims. Because accidents are never planned and family members are rarely available during the important early treatment period, we would like to offer the treatment to patients who cannot sign a consent for themselves. The patients who would receive the treatment will be critically ill and unable to sign consent because of their life-threatening injuries. The treatment will not change the way the doctors treat patients. All patients will continue to receive blood and other intravenous fluids as required. The study drug will be in addition to the regular treatment.

The U.S. Food and Drug Administration (FDA) requires new drugs and treatments to be proven effective in human volunteers before the drug or treatment can be marketed. The FDA has recently ruled that under strict circumstances, unconscious patients whose life is in danger (and no family members are present to give consent) may be given experimental treatment if there are not other treatments available which have a good chance of success. The patients who might receive the drug and their families will be notified at the earliest opportunity of their inclusion in the research study.

We believe injury victims with massive loss of blood meet all of the conditions set forth by the FDA. That is, these patients could be included in a study without informed consent, because they would be too sick to understand and sign. The FDA requires the University of Cincinnati and the University Hospital to inform the public of this research study and that patients would be enrolled in the study without informed consent. The FDA also requires that we receive public input before a decision is made to begin the research study.

We invite you to communicate with us on this subject. Please write us at the following address:

University of Cincinnati
 Department of Surgery
 Trauma Research
 231 Bethesda Avenue
 Cincinnati, Ohio 45267-0558

or call the Research Office at SB-SSB-330,

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University Hospital Study of a Blood Substitute for Injured Patients with Severe Blood Loss

The University of Cincinnati and University Hospital have been conducting a study of a new treatment for patients with severe blood loss (automobile accidents, falls, etc.) The treatment developed by Baxter Healthcare Inc. can be used as a blood substitute during emergency surgery. This treatment has been used in over 350 patients worldwide.

The University of Cincinnati and University Hospital would like to make this treatment available to accident victims. Because accidents are never planned and family members are rarely available during the important early treatment period, we would like to offer the treatment to patients who cannot sign a consent for themselves. The patients who would receive the treatment will be critically ill and unable to sign consent because of their life-threatening injuries. The treatment will not change the way the doctors treat patients. All patients will continue to receive blood and other intravenous fluids as required. The study drug will be in addition to the regular treatment.

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University of Cincinnati
Department of Surgery
Trauma Research
231 Bethesda Avenue
Cincinnati, Ohio 45267-0558

or call the Research Office at 513-558-3850.

Attachment 6

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Blood Study Video
WCPO-TV
Channel 9, ABC affiliate
Date: 8/1 8/97, 5: 00p.m. News

000-000007

Newsroom Scene:

Newsman (Name not provided): "...and still to come your way ABC 9 --Can fake blood change emergency medicine."

Newsman (Name not provided): "Well a Cincinnati hospital wants to find that out. We'll look at the study and tell you why doctors find it very exciting."

Hospital Scene:

Bloody patient being rolled on gurney. Title across screen reads "COMING UP FAKE BLOOD"

Newsroom Scene:

Newsman: "Tonight, the University of Cincinnati is prepared to start testing a new kind of artificial blood, if the public doesn't object."

Newsman: "Well Price is here to give us the local update on the story we first told you about this past spring."

Bill Price: "In May we told you about this artificial blood, they prefer **you** calling it blood replacement in some cases. Well some traumatic accident victims may get blood flow restored in as much as an hour sooner if (the) University Hospital goes ahead with tests on a new man-made blood replacement. You see the emergency room could be just one of the nine in the nation testing a kind of new temporary blood replacement called HemAssist."

Hospital Scene:

Bill Price continued: "Now the chemical solution contains hemoglobin **carry(ing)** vital oxygen through the body after a critical injury has severely reduced or cutoff blood flow."

Dr. James Hurst, U/C Surgery Dept.: "We don't have to worry about typing this material the way we do conventional blood products. For example, we know it has longer shelf life and we know it is safer. Although the American blood supply is extraordinarily safe we know that this compound is even safer than the American blood supply because it's been heat treated."

Newsman: "Now for the first time the University Hospital researchers are asking the public for opinions on this proposed research before they go ahead with it. You can call the UC Surgery Research Department at 558-3850, with your opinion on this blood replacement testing. 558-3850."

The following is flashed across the screen, "Blood Test Comments 558-3850 UC Surgery Research Office"

Newsman continues: "The hospital will not decide to go ahead with the study for at least another three months."

Attachment 7



the oldest of the skeletons appear to have Eurasian features, as opposed to the northern Asian features common to modern American Indians, that are characteristic of later-date remains.

No one knows whether the apparent dissimilarity means the earliest inhabitants came from a different place or population, or whether their appearance simply evolved over time.

But the issue is potentially explosive because it raises questions about the prehistoric foundation of American Indians in their ancestral lands. More immediately, it lays

Mr. Schneider said. "What's going on here is not a question of whether Native Americans can believe and follow their traditions, but it's a question of whether all of the rest of the country can be required to follow their traditions."

In one of the first federal court opinions to explore issues raised by the latest finds and by the Native American Graves Protection and Repatriation Act — which requires custody of Indian burials to go to local tribes — a U.S. magistrate in Portland, Ore., in June sharply reprimanded the U.S. Corps of Engineers for moving to hand over

000-000008



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HEART ON FIRE

751-0606

APOSTLES of the HOLY SPIRIT
2709 Woodburn Ave. Cincinnati, Ohio 45206

University Hospital Study of a Blood Substitute for Injured Patients with Severe Blood Loss

The University of Cincinnati and Wiry Hospital have been asked to participate in the study of a new treatment for patients with massive blood loss following trauma (automobile accidents, falls, gunshot wounds etc.) The treatment developed by Baxter Healthcare Inc., is a patented product which can serve as a blood substitute during emergency treatment. This treatment has been used in over 350 patients world wide.

The University of Cincinnati and University Hospital would like to make this treatment available to accident victims. Because accidents are never planned and family members are rarely available during the important early treatment period, we would like to offer the treatment to patients who cannot sign or consent for themselves. The patients who would receive the treatment will be critically ill and unable to sign consent because of their life-threatening injuries. The treatment will not change the way the doctors treat patients. All patients will continue to receive blood and other intravenous fluids as required. The study drug will be in addition in the regular treatment.

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We invite you to communicate with us on this subject. Please write us at the following address:

University of Cincinnati
Department of Surgery
Trauma Research

Attachment 8



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Posted at 6:19 p.m. EDT
Monday, August 18, 1997



[Knight-Ridder
Newspapers](#)

Researchers want public's opinion about artificial blood

CINCINNATI (AP) -- Medical researchers want the public's opinion about whether doctors should put artificial blood **into** patients when the **real thing** is not available and **there** isn't time to obtain consent in an emergency.

The public's **response** will be a major consideration in whether researchers at **the** University of Cincinnati College of Medicine and University Hospital proceed **with the** proposed **study**, **university** spokesman Rick Smith said Monday.

It would **be** a year-long **study** with about 30 patients. The **Cincinnati** researchers plan to **run advertisements** in **Cincinnati** newspapers Wednesday to find **out** whether **the** community would support the study, including "the idea of **using artificial** blood in patients **without** their **consent**."

The medical school's investigation review board, which **is** responsible for all clinical **trials** done **at** the school, **will** use **the** public comments to help decide whether **to** do the **study**, officials said. They declined Monday to predict when **the** board will decide,

"If it comes out (as) **strong sentiment** against, we won't do **the** study," **Smith** said.

The artificial blood is called Hem Assist. The manufacturer **is** **Baxter** HealthCare Corp. of **Deerfield, Ill.**

Researchers are testing the red-colored liquid, made from human **blood stored** in **blood** banks, to determine whether it can **save** the **lives of** critically injured **patients** when real blood is **not** immediately available. **Baxter** HealthCare **is** coordinating the studies. subject to U.S. Food and Drug Administration **supervision**.

The study is to involve at **least** 850 patients. **Some** scientists have **argued** there could **be** **health** risks because **the** product raises blood pressure through complex blood vessel **changes**.

The FDA is also considering allowing a similar **study of** **Northfield** Laboratories Inc.'s **PolyHeme**, a competing product.

To find **out** how well **artificial** blood works, researchers need to **try** the **product** in real trauma victims

The product is a chemical solution containing large amounts of hemoglobin, the oxygen-carrying protein normally found in red blood cells. Unlike regular blood, the product can be used in anybody without doing cross-match tests to check for blood type -- which can take an hour.

At least six other medical centers have enrolled patients who have consented to participate in the studies, said Dr. Fred Luchette, a trauma surgeon who would be the lead researcher for the Cincinnati study. He said he knew of no other test sites in Ohio.

"Myself, and my colleagues at UC, are very excited because we think it offers another chance for critically injured patients to survive their trauma," Luchette said.

Luchette said that about 350 patients have been given it in other studies, and they have tolerated it well. He said monitoring has shown that some patients exhibit elevated enzyme levels, which could indicate problems with liver functions, but that the levels have been found to drop quickly to normal reading.

The patients would be among the most severely injured who come to University Hospital's emergency department. The injuries will be so severe that only 50 percent of patients would normally be expected to survive, Luchette said. The hospital receives about 100 such patients a year.

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Attachment 9

1

1. NEXT MEETING
5 SEPTEMBER 1997

JUDICATORY URBAN STAFF

NOTES

6 JUNE 1997

PRESENT: Chandler. Choquette. Grady. Holm. Hyvonen. Neuroth. Rado

REGRETS: Abrams. BOSS. Dalton. Simonton

ABSENT:

X.

PUBLIC HEAL'Y

Waiver OF Informed Consent

Dr. Fred Luchette, Department of Surgery
University Hospital

(The Reverend **Damon** Lynch, Jr., new *member* of Board at University Hospital. referred Dr. **Luchette** to **MAROC** as way to **access Cincinnati** religious **community**. **Holm suggested he come** to Judicatory Urban Staff as quickest way to **access** Judicatories.)

Dr. Fred Luchette explained that he (and the University Hospital **team** of which he is a **part**) need to "disclose" to the public, as widely as possible, a research study they will be doing with reconstructed blood in which they will **not** be able to **get "informed consent"** from the patient or family.

Trauma one of leading **causes** of death. Following accident. patient **brought** to hospital, often in "**hemorrhagic shock**" (Mood pressure **<90**, heartbeats **>120/minutes**). Doctors **give** IV fluids. **If** decide need blood, give **O-Negative**. **because it doesn't have side effects with other blood** types.

In this test, doctors **will** give

- sane patients O-Negative blood + **DCLHb**
- other patients O-Negative blood + saline solution.

All will **get** present treatment: O-Negative blood. Doctors will know who **got** what. Start within 1 hour, **give twice** within two hours. In **these** kinds of accidents, patient usually unable to give consent, **family** members don't arrive until later.

DCLHb is made from outdated **blood, more** than 120 days **old**. It is screened for infections, treated to stabilize the **hemoglobin** (that carries oxygen), and pasteurize. ["up-dates" out-dated **blood!**]

A **small amount** restores **blood** pressure, and carries oxygen. Doesn't require refrigeration.

Worst possible **side** effects are mild jaundice-like effect for 8-10 days. **Will** seek inferred **consent** as soon **as possible**, follow-up **patients** for 2S days.

Has been **some** reluctance at University **Hospital** to enter into test because of **informed** consent **problem**. FDA requires us to make **community** aware of what we are doing. University Hospital is one **of** several hospitals **across** nation involved in this test. **We** in Cincinnati are bending over **backwards** to **make community aware**. will do public **service announcements**, television, **public meetings**. **This** is our 1st meeting.

After discussion. Judicatory **Urban** Staff suggested **as** follow-up

- Luchette send **MAROC** draft of letter **and** bulletin board **announcement** to be sent Out.
- **Helm** will **edit** to make accessible, **understandable** to **religious** congregations **and** send back to Luchette.
- Northern Kentucky Interfaith **Commission**, Council of **Christian Communions**, **and Jewish Community Relations** Council will send Dr. **Luchette** their mailing lists. (**Unless** he wants to use **MAROC's** as "abridged edition.")

University Hospital

234 Goodman Street
Cincinnati, Ohio 45257

Public Relations & Marketing

Medical Arts Building
222 Piedmont Avenue
Suite 4300
Cincinnati, OH 45219
Phone: (513) 475-7920
Fax: (513) 475-7922

NEWS

For Immediate Release
August 27, 1997

Contact: Rick Smith

University Hospital To Study A Blood Substitute For Injured Patients With Severe Blood Loss

Cincinnati --The University of Cincinnati and University Hospital have been asked to participate in the study of a new treatment for patients with massive blood loss following trauma (automobile accidents, falls, gunshot wounds, etc.). Developed by Baxter Healthcare Inc., the treatment is a patented product which can serve as a blood substitute during emergency treatment. This treatment has been used in over 350 patients world wide.

The University of Cincinnati and University Hospital would like to make this treatment available to accident victims. Because accidents are never planned and family members are rarely available during the important early treatment period, we would like to offer the treatment to patients who cannot sign a consent for themselves. The patients who would receive the treatment will be critically ill and unable to sign consent because of their life-threatening injuries. The treatment will not change the way the doctors treat the patients. All patients will continue to receive blood and other intravenous fluids as required. The study drug will be in addition to the regular treatment.

The U.S. Food and Drug Administration (FDA) requires new drugs and treatments to be proven effective in human volunteers before the drug or treatment can be marketed. The FDA has recently ruled that under strict circumstances, unconscious patients whose life is in danger (and no family members are present to give consent) may be given experimental treatment if there are no other treatments available which have a good chance of success. The patients who might receive the drug and their families will be notified at the earliest opportunity of their inclusion in the research study.

We believe injury victims with massive loss of blood meet all of the conditions set forth by the FDA. That is, these patients could be included in a study without informed consent, because they would be too sick to understand and sign. The FDA requires the University of Cincinnati and the University Hospital to inform the public of this research study and that patients would be enrolled in the study without informed consent.

-more-

The FDA **also** requires that **we** receive public input before a decision **is** made to begin the research **study**.

We invite you to communicate with us on **this** subject. Please write **us at** the following address:

University of **Cincinnati**
Department of **Surgery**
Trauma Research
231 Bethesda Ave.
Cincinnati, **Ohio** 45267-0558

or call the **Research** Office at (513) 558-3850.

Attachment 11



Radio program WCIN
 Doctors: **Luchette/Davis**
 10/28/97

Beginning of program was not **recorded**, discussion begins:

Lincoln Wier: "...and Dr. Ken Davis, they're Trauma Surgeons at **University** Hospital. We're talking about this study of a blood substitute for injured patients with severe blood loss. This is not in effect herein **Cincinnati** but they're doing it in a **few** other **cities** around the **country**. And what happens **is** -why don't you explain to us exactly what this study is about and what has to happen before you **will** become a part of this if **it** ever takes place."

Doctor: "Sure, thank you Mr. Weir. This study involves using a new medication for patients that are bleeding to death and their hanging on life and death situations when they arrive at the hospital. One of the problems currently is that we give blood and there is risk with blood and this **mediation is** made from old blood but it's safe it's been used in about 350 patients throughout the country in other studies. For this study the **red issue is** that the patients are so sick when they get to the hospital **if I** asked them for permission to participate in the study they are so **sick** that they can't give what we **call** informed consent so what we're really here to talk about is the issue of waiver of **informed consent** to participate in this study."

Wier: "Now have there been any side **affects** from people who use this blood substitute?"

Doctor: "Very minor ones, probably the most **common one is there is an** mild elevation in blood **test to** evaluate how their liver **function is** and **also in pancreatitis**, an inflammation of the pancreas gland. However once the mediation is stopped all of these side **affects** have resolved, and there's been no long term problems for the patients."

Wier: "So is it like a transfusion you give them or at this point when you say okay we **can** use this blood substitute you immediately give them **a** blood test then a **transfusion** or -"

Doctor: "We don't have to give them a blood test for it."

Wier: "You **don't**, you don't"

Doctor: "And the advantage of this is that we can give it quicker than we can give a **transfusion** because we have **to** cross-match somebody to get their right blood type, this -it doesn't matter what blood type you are. It's **there**, immediately **available**, rather than waiting 20 or 30 minutes to get a blood type and get blood. The other advantage is **because** of the processing of it, it is much safer -that it doesn't transmit certain diseases, viral **diseases**, like hepatitis or AIDS."

Wier: "And I'm sure a lot of communities probably look at this and say yea we want this done here in our city. Now have you had any communities say no, we don't like this or any religious groups who are opposed to this?"

Doctor: "Well, religions (persons) that are opposed to blood transfusions will not receive this."

Wier: "Okay, Okay"

Doctor: "There are certain religions where people are opposed to using blood and they would not be --they would be excluded from **receiving** this."

Wier: "Even when it's a matter of life and death. If the guys unconscious of shot -gunshot wound and he's on the brink of death."

Doctor "If we know their religion is opposed to that, even if they're on the brink of **death**, we will not give them blood and **would** not use this product either. If we don't know, and we're in the process of **trying** to save somebody's life we'll give it not knowing. But we wouldn't knowingly give this or any other product to somebody that has a religious opposition to it."

Wier: "Now course you know race always come into it. A lot of people say well if you're in a black community normally your **gonna receive** a lot of gunshot wounds and stabbings and things like that, this is just an experiment you're **gonna** use blacks as **guinea** pigs for. I'm **sure** you've heard that."

Doctor: "Well, we haven't heard **that**, but we've expected that and what we did was we looked into our own computer registry of **all** of our trauma patients. The person that is most likely to be the recipient of this is a **19 yr** old white male, that has been involved in a oar accident. Because that's most of what we see. 85% of the trauma that we see at the University Hospital is what we call blunt trauma and the vast majority of that is oar accidents. So actually **a black male** would probably be the least likely to get it where a young white male is **gonna** be the most likely."

Wier: "Now what has **to take place** before this will be enacted at the University Hospital. What has to take place from this point on."

Doctor: "Right now Mr. Weir, **we're going thru** a **process** with the investigational review board at the University to go thru a process which the FDA and **NIH** has established for this type of study involving public **disclosure** and community consent and that's why were here talking to you today to get community's **feedback** in what they think about this study and giving up the right to give consent to participate in a study."

Wier: "So how would people who want to get involved in this and if they're opposed to it what would they have to do."

Doctor: "What we would like to do is ask anybody who has any comments or questions to call our office at 5583850 if no one is there to answer the phone they'll get **an** answering machine to take the message and we'll get back to them as soon as possible."

Wier: "Okay, I tell you what we'll take some calls here... **if** you want to call in and respond, **we** want to know how you feel about this happening at the University Hospital. Are you in favor of it

or if you disapprove of it...we'll hear how Cincinnatians feel about this study being done at the University Hospital...do you want it to take place or not? I mean it's experimental BUT it could save lives. What do you think? . . .

(Portion of the show not recorded, discussion begins in mid-call)

Caller #1: "...that it's not really **been**, and I would **liked** Lincoln to have really done a detailed show because the information I **received** was so detailed on who, **what, when**, and how they would give this and again we must look at this as test project and **wemust**, ya know, just **factor** in human factor into this the --truly are anyone going to try to contact anyone in a timely manner or is there another testing mechanism for African American people."

Wier: "**Well** he can answer the who, what, where, why, and when. Who will receive this, I thought we answered --go ahead and answer that."

Caller #1: "**No** what I'm saying is and I'll be more than happy **Lincoln** to give you the **information** that was give tome but there were a lot of different circumstances of who would get it and who wouldn't and that would take along time to go **thru** according to what the **woman told me** on the phone, cause I talked with her for approximately 30 minutes. She went thru various things of who would and wouldn't and under what conditions and etc. I'm just saying that I just think this is being done real quickly I think that its not - **ya** know -it showed me **from** those ads that you truly **did** not want to **inform** the public by putting it on the science page in very small print and coming on the show for 15 min. to tell us what a wonder thing this is. **Let's** look **at history** for African Americans. Testing and using us as Guinea pigs has been part of the process and **I** think we must truly not be a Guinea pig again for University Hospital which just got out of one jam **over** testing of **radiation** which included not only **African American people** but **other people** too."

Wier: "Okay, holdup, let him respond to that."

Doctor: "**Ma'am**, thank you for your comments. We've been working with the investigational **review board** for six months thru this process of public disclosure **and community consent**. This study is not about the **safety** of the **medication**, the mediation is very **safe** to give the patients. This study is looking at patients that are severely injured that with **conventional** management they have a 40?? mortality and possibly with the addition of this drug this **new** artificial blood we may reduce that mortality to 30?! so we're talking about truly **saving** lives **white, black**, any type of patient that would come into University Hospital after some type **of injury** whether its a car accident or stabbing or gunshot wound."

Caller #1: "**Again, I** just think **that, I** hope the listeners are listening real strongly that I would not want to give card **blanc** permission to anyone to do something to **me** without my giving permission or family member giving permission."

Wier: "Even **if it could** save your life?"

Caller #1: "For 30- 40%, I'll take that 10% risk."

Doctor: “**Not** everyone will get this without **their** permission. And what we’re talking about is a **small** group of people that are unable to give permission because they’re unconscious and we’re unable to get a hold of anybody in their family. For example, we get a number of people we don’t even know their name, so it’s hard to contact anybody in terms of next of kin --to do anything, whether its to operate on them as an emergency or to give them conventional treatment much less anything like this that would **be** investigational so that’s a small group of people we’re talking about. Most - inmost instances we expect that we will be able to ask individuals or **family** members for their permission yes or no **todo** this. The other thing is only about 50% of the people will get this. There are 50?! that this 50% that will get regular intravenous fluids such as saline instead of this so we can compare the two.”

Caller #1: “**Well**, if you think you’re going to get such a high percentage of people to give you permission then why do you need to test on people who don’t give you permission.”

Doctor: “Because those are probably the people that will need it the most and derive the most benefit.”

Caller #1: “And again you use the “possible” again this is still the testing process. **And** all I’m saying to folks is, and **to** you too, and I think maybe individually you all are very sincere, but I just have to look at the **history** of America. I have to look at the fact that I don’t think the advertisement was sufficient even with not everyone reading the paper -truly wanted to reach everyone, it **wouldn’t have** been hidden on the science page in very small print -and I have a copy of that if you’d like **to** see it. **But again, ya know**, I’m **gonna** leave **cuz** I’m sure there’s other callers, I think we still have to look at issues -“

Wier: “But I think this show’s a good first step and I’m sure they’ll be on other radio shows throughout the city to bring this to the **forefront!**”

Caller #1: “Oh I’m sure Lincoln because I actually suggested some other stations -that they told me they were **gonna** be **on CIN** -and I suggested some other stations so that-”

Doctor: “We asked to come on this show, it wasn’t that we were invited.”

Caller #1: “-and so I’m —so **I’m, well** I was told by the person that they had someone had suggested that they come on **CIN** and **I** said everyone’s not available to listen to Lincoln in the day, you really need to do better publicity on this so there aren’t any incidents down the road or someone saying you gave me something and **didn’t** know anything about it. And again **I** just have to **reinnovate** that we have **to** look at history we have to look at the **recent** thing on 60 minutes on the Cleveland Clinic **and...donor** issue of people’s organs of being **preserved** versus treating them. I still think that in America with real **life** human beings making decisions about our lives, we need to look at it and I think that permission should always be given and if you’re gonna have it a higher rate of 50% for permission that should give you more than enough data to prove that this fake blood is good or not and I think you should stay away from the other because University Hospital’s history on testing folks on telling them one thing and doing another is not very good. Thanks Lincoln and good bye.”

Wier: "Alright, thanks for your call. Alright so what are some of the other cities that maybe should could call one of the other local hospitals in another city just to get their test results or something ya know just to ease her mind. What are some of the other cities this test is being done in?"

Doctor: "One is **Allentown**, PA at Lehigh Valley Hospital, the other is the **Medical Center Delaware** in Delaware and the Carolina hospitals down in South Carolina."

Wier: "Well, like you say, I'm sure you're **gonna** hear opposition to this anytime you do this type of study people are going to be suspicious on what's going on, so I'm sure -but like I said you'll be on other stations I'm sure before this is approved for the University Hospital it's **gonna** --it'll be **well** publicized I'm sure **because** you have to do so much advertisement of this before you can even start."

Doctor: "Sure."

Wier
Doctor: "History is why we're here, I think what she's talked about is the history of University Hospital in the past and the perception people have of University Hospital and that's **why** we're here. If you look at the radiation study."

Doctor: "Those things were done in a **different** era and I think things are handled differently now and this is one of the reasons **we're** here is to be **upfront** and open about the fact that we're interested in doing this and to hear what people's **concerns** may be."

Wier: "Alright let's go to the phones,..."

Caller #2: "I just wanted to commend that sister without the respect to the ones that are there speaking on this -the blood substitute. I just want to commend that sister, that's all. I just want to thank her for her for her **comment**, thank you."

Wier: "So I guess you agree with her, you're not in favor of this."

Caller # 2: "That's **all** I want to say. Thank you."

Wier: "Okay. Non **committal** there, she'll be a great **politician then**, I believe. But, we want to thank you for stopping by. Is there a number that people can call to **ahh--**"

Doctor: "Yes, Mr. Weir we invite your listeners to **call** us with any questions or seeking any other **information 5583850**"

Wier: "An what -how can they -- **if they're** not in favor of this they can tell the person that the calls we monitored and"

&=&-

Doctor: "We're keeping a log of all phone calls, the individual placing the call, their comments and then we are presenting those to the investigational review board. "

Wier: "Okay what about letters or **organizations as** a whole who want to express their feelings on this **can** they send you a letter or something?"

Doctor: They **can** send us a letter, or they can just **cal**. Probably the simplest thing is just to call that number 558-3850."

Wier: "Alright, well thank you **for stopping** by and **we** hope we put out enough **information** for people to get an understanding, **atleast** a general **understanding**, on what could take place at University **Hopsital**, what's going on in some other cities around the country and it looks like it will be another avenue for saving a life. And like you said you're gonna get the regular care that you would normally get this is just a stop gap between life and death. **Alright**. Thank you for joining us and tell **Ms.Davis** I said hello, please."

Doctor: "Thank you for having us."

Attachment 12



DCLHb Traumatic Hemorrhagic Shock Research

<u>DCLHb Description</u>	<u>What is DCLHb?</u>
<u>Preclinical Summary</u>	Diaspirin Crosslinked Hemoglobin (DCLHb), the investigational biologic being tested in this trial, is a purified and stabilized human hemoglobin solution manufactured by Baxter Healthcare Corporation. Hemoglobin is the protein in red blood cells that carries oxygen.
<u>Clinical Program Summary</u>	
<u>U.S. Trauma Study Overview</u>	<u>What is the purpose of this web page?</u>
<u>U.S. Trauma Study Design</u>	This web page is provided as a resource to assist hospitals and investigators in meeting the requirements for community notification of planned research and public disclosure of the potential risks and benefits of the current research of DCLHb in treating traumatic hemorrhagic shock, as specified in the U.S. Department of Health and Human Services (HHS) Code of Federal Regulations (title21 CFR section 50.24) entitled "Waiver of Informed Consent Requirement in Certain Emergency Research."
<u>Informed Consent Information</u>	
<u>Frequently Asked Questions</u>	<u>What is the title of the research protocol?</u>
<u>Search This Site</u>	"The Efficacy Trial of Diaspirin Crosslinked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock
<u>Sign the Guest Book</u>	

Request information: info@dclhb.er.uic.edu
 Feedback to webmaster: webmaster@dclhb.er.uic.edu

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DCLHb Preclinical Summary - 0000023

In the last 10 years, more than 100 major preclinical studies have been performed with DCLHb. Over 50 different academic and contract laboratories in North America, Europe, and Australia have participated in preclinical research to investigate the pharmacology, physiology, safety, and efficacy of DCLHb. DCLHb has been studied in animal models of hemorrhagic shock, sepsis, stroke, myocardial infarction, balloon angioplasty (PTCA), burn injury, and trauma. These include studies looking closely at the safety of DCLHb and have shown that DCLHb maybe safely infused into humans.

The knowledge gained from preclinical studies has led to the design of clinical trials that will determine the ability of DCLHb to safely and effectively treat human illness and injury. All of the preclinical studies performed to date have been approved by the review committees of the participating universities.

[Back to the DCLHB Research Web Site](#)

DCLHb Clinical Program Summary

Of the more than 850 patients who have participated in DCLHb studies to date, about half have received DCLHb. The clinical studies already have involved more than 25 hospitals or universities in the U.S. and 8 other countries. During the 5 years of human clinical work, DCLHb has been studied in many different clinical settings, including hemorrhagic shock, trauma, stroke, kidney dialysis, overwhelming infection, critical ICU illness, acute anemia, and peri-operative use, including orthopedic, cardiac, abdominal aortic repair, and other major surgeries. All human trials include close monitoring for patient safety and all studies were reviewed by the appropriate regulatory agencies and the Institutional Review Boards (IRBs) or Ethics Committees (ECs) of the participating centers.

- Overall, the clinical trials completed so far indicate that DCLHb is well tolerated by the various patient populations tested. The most commonly seen side effects include elevation of blood pressure, red discoloration of the urine, and yellowing of the skin.

In addition, isolated cases of patients with inflammation of the pancreas, or pancreatitis, have been reported in patients receiving DCLHb. In some patients who have received DCLHb in doses greater than 500 mL, a jaundice-like yellow coloring of the skin or eyes has been seen. The coloring appears to be related to the metabolism of DCLHb into bilirubin as well as passage into the tissues of the colored protein. The yellowing effect may last about three days and has not been associated with liver or other medical problems. An increase in blood pressure has been observed consistently in patients who have received DCLHb.

The initial clinical trial of DCLHb to assess its safety in shock and trauma patients studied the infusion of saline (salt water) or DCLHb in

139 patients (71 of the patients, 51 %, received DCLHb) with mild to — severe shock. The trial was divided into three dose levels, 50 mLs, 100 mLs, and 200 mLs. Each dose level included at least 40 patients (approximately half received saline and the other half received DCLHb). In this trial, the number of patients who died and the rate of side effects was not greater in patients who received DCLHb.

DCLHb has been extensively studied in heart surgery patients and is currently being studied in selected orthopedic surgery and abdominal aortic repair patients to test the safety and effectiveness of DCLHb in preventing blood transfusions. DCLHb also is being tested in a hemorrhagic shock trial in trauma patients in Europe, where DCLHb is transported by ambulances for physicians to use at the emergency scene.

[Back to the DCLHB Research Web Site](#)

U.S. Trauma Study Overview

Trauma is an important public health problem in today's society. The effect of severe trauma is immediate and catastrophic with approximately 150,000 people dying each year and many others suffering prolonged illness due to trauma injuries. Advancements in trauma care are necessary in order to improve the rate of survival and complete recovery of people suffering from severe traumatic injuries.

The purpose of this research study is to find out how well this new hemoglobin solution works in treating or preventing the harmful effects from the blood loss and shock that occur with severe traumatic injury. The harmful effects of shock can include prolonged illness or death. This research study will include only severely injured trauma patients whose death rate may be as high as 40% despite receiving the best medical treatment available. In this study, all of the patients who participate will receive all of the currently available therapies known to save lives following injury. Those patients who are given **DCLHb** will receive it as additional therapy to the best standard therapies available. **DCLHb** will be studied to see if using it prevents death and prolonged illness in patients who receive it. The standard treatment for severe trauma includes giving large volumes of fluids and transfusion of blood through a vein. Surgery is often necessary to stop the bleeding and repair the injuries. These standard therapies will be made available to all of the patients treated in this research protocol, including those that receive the **DCLHb**. The new treatment includes giving 500 mLs (1 pint) to 1000 mLs (2 pints) of **DCLHb** within sixty minutes of arriving at the hospital. This is in addition to any standard treatment required, including surgery.

- If this study shows a clear benefit and little or no harm to patients, this investigational solution may be cleared by the U.S. Food and Drug Administration (FDA) for use in patients who suffer from shock as a

result of severe injury. As with any clinical trial, safety also will be studied.

[Back to DCLHb THS Research Page.](#)

U.S. Trauma Study Design

In this trial, the patients will be randomly (like a flip of the coin) assigned to receive either DCLHb or an equal amount of saline (a salt solution currently used as a treatment for shock). The order of assignment will be determined prior to any patients being entered into the study so that neither the patients nor the patients' doctors can choose which solution is given.

Saline is used during the emergency treatment for shock patients to help replace the blood loss due to the injury. The patients who receive saline in this study will be the control group. These patients will not receive DCLHb. All patients will receive the best known current therapy for shock. The outcome (survival and illness) of patients who receive saline will be compared to the patients who receive DCLHb to see if the addition of DCLHb to the current therapy improves survival and decreases illness.

This study will take place at approximately 35 trauma centers across the United States, each of which will treat 20-30 patients in the protocol. Approximately 850 patients will participate in the study. Participation in this protocol will not interfere with the timely delivery of any of the lifesaving therapies currently available for treating severe traumatic shock including the immediate infusion of resuscitation fluids and blood, as well as emergency surgery if needed.

Primary Clinical Benefit Measurement

This study is designed to determine whether there is a decrease in 28 day mortality, or a smaller number of deaths 28 days after treatment, in patients treated with DCLHb

compared to those in the control group (not receiving DCLHb).

Secondary Clinical Benefit Measurement

This study is designed to determine whether or not there is a decrease in serious illness due to the harmful effects from the blood loss in patients treated with DCLHb compared to those in the control group (not receiving DCLHb).

This study is also designed to determine whether there is a decrease in 24 hour lactate levels in patients treated with DCLHb compared to those in the control group (not receiving DCLHb). Lactate is a by-product of shock caused by a lack of oxygen being delivered to tissues and cells.

Lastly, this study is designed to determine whether there is a decrease in 48 hour mortality, or a smaller number of deaths 2 days after treatment, in patients treated with DCLHb compared to those in the control group (not receiving DCLHb).

Patient Population

The patients entered into this study will be a very small number of the total trauma patients who are treated in trauma centers across the U.S. Most will have been treated by emergency medical personnel prior to getting to the hospital and many will still be in shock despite the emergency care outside of the hospital. Patients will participate in the

study only after meeting strict entry criteria. These criteria are designed so that only the most severely injured patients who have serious shock and lack of blood flow due to bleeding will participate in the study. These patients are at the greatest risk of death. Patients may be males or females who are believed to be at least 18 years old. Patients with severe head injuries or whose heart has stopped in the hospital will not be entered into the study.

DCLHb or the control solution (saline) will be given to the patient no later than 30 minutes after meeting these strict criteria and within 60 minutes of arrival at the emergency department.

Study Procedures

All standard therapies and procedures normally used to treat patients with severe shock will be provided. These standard therapies include the immediate infusion of resuscitation fluids and blood, as well as emergency surgery if needed. In addition to standard therapy, patients will initially receive either 500 mL (1 pint) of DCLHb or saline. The solution will be given through a vein, similar to the way in which blood is provided to these shock patients.

After the first infusion of **DCLHb** or saline, the doctor will evaluate the patient's condition and decide if additional infusions of fluid are needed. Up to two additional 250 mL (½ pint each) of DCLHb or saline can be given within 60 minutes after the start of the first infusion in order to stabilize the patient's shock condition. Strict guidelines will be used to decide whether the **infusion** should be stopped at any time in order to maximize the patient's safety.

During the study, the doctor will collect information from the patient through physical examinations and laboratory tests including urine specimens, blood withdrawn from a vein, and blood withdrawn from an artery. These procedures are not significantly different from the

usual tests done to evaluate and treat a patient in this severely ill condition. Each blood sample drawn will be 5 to 15 cc in volume (between a teaspoon and a tablespoon sized sample).

The healthcare team will also evaluate the patient's vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and effort) often during the first 48 hours of the study. The patient will also have blood collected and vital signs evaluated at days 4,7, 10, 14,21, and 28 after infusion. The patient's participation in the study lasts for a total of 28 days.

Informed Consent Procedures

The consent procedures followed in the protocol will follow the Federal Regulations set forth in 21 CFR 50.24 "Exception from informed consent requirements for emergency research. "

Please see the section entitled Informed consent (add hot link here)

Safety Monitoring

An independent Data Monitoring Committee (members not affiliated with Baxter Healthcare or the conduct of the study) will be established in accordance with the Federal Regulations. Ongoing safety monitoring will be independently performed by this committee during the enrollment of study patients. If major safety concerns arise, the study can be changed so that patient safety can be maximized.

Potential Risks

As with most medical treatments, it is possible that DCLHb could cause side effects. Reactions or discomforts have been reported in previously completed animal and/or human studies with either DCLHb or other experimental hemoglobin solutions under development by

other groups.

000-000032

Based on reports about ALL hemoglobin solution products, possible reactions that may occur are:

stomach pain (gas, bloating), stomach cramps, constipation, nausea or vomiting shortly after infusions

back pain or muscle aches

a temporary general weakness or discomfort, headache

a temporary red discoloration of urine caused by hemoglobin (the protein found in red blood cells that carries oxygen)

a temporary elevation (rise) of certain laboratory test results; for example: proteins and enzymes that could indicate damage to organs such as the pancreas or liver, or to muscles

a temporary inability to do certain laboratory tests accurately

a temporary rise in blood pressure

a temporary jaundice-like yellow coloring of the skin or eyes (related to the metabolism of modified hemoglobin into **bilirubin** as well as passage of the colored protein into tissues). The yellowing effect may last approximately three days and has not been associated with liver or other medical problems.

a temporary abnormal kidney function

a temporary increase in the time it takes for blood to clot

a possibility of small areas of cell damage in heart muscle,

— liver, or kidneys (only seen in some kinds of laboratory animals)

allergic reactions such as chills, elevated temperature, or skin rash

DCLHb has been studied in over 400 patients so far. Besides patients with severe traumatic shock, trials have included patients undergoing various surgical procedures including cardiac surgery, orthopedic surgery and abdominal aortic repair, patients on renal dialysis, and patients suffering acute ischemic stroke. However, there maybe risks relative to the use of this product that cannot be anticipated from such prior human use and the use of DLCHb could cause reactions (side effects) that are unknown as yet. Also, patients with severe trauma currently are treated with a number of therapies including surgical and drug therapies. These currently used treatments carry substantial risks — in and of themselves, including death and permanent injury.

Because DCLHb is an investigational solution and the effects in pregnancy have not been determined, risks to an unborn baby are unknown at this time. DCLHb will not be given to patients who are known to be pregnant.

The risks associated with drawing blood include pain, bruising, lightheadedness, and occasionally, infection. These risks are usually small. Some blood drawing will be done through already-existing catheters (tubes) left in the blood vein or artery. This greatly reduces the painful part of repeated blood drawing. Insertion of a catheter (tube) into a blood vein or artery will only be done if needed as part of the usual care of the patient. This practice is typical for patients who — are critically injured.

Benefits

Patients who receive DCLHb may have an increased chance of survival or of avoiding serious prolonged illness. However, there is no guarantee that this solution will benefit those who receive it. The potential benefits to all of the study participants include extensive medical testing and examination. Another important potential benefit is that the information gained from this study could help patients who need this type of medical care in the future.

Additional Costs

Special laboratory studies will be done on the blood samples at the expense of the researchers and at no extra cost to the patient. There will be no additional cost to the patient for participating in the research protocol beyond the costs of the standard medical care required to treat the patient's condition.

Alternative (Other) Treatments

It is important to note that all patients who participate in this study will receive the best known current therapy for traumatic hemorrhagic shock, including the immediate infusion of resuscitation fluids and blood and emergency surgery, if needed. In other words, being a patient in this study will not hinder the delivery of any of the lifesaving therapies that are currently used in patients with severe shock.

The alternative to participating in this study, is to receive the standard medical care that critically injured trauma patients currently receive in the emergency setting.

Additional Information

Besides the risks and side effects described, additional risks that are not currently known may arise. If additional side effects are

discovered, the sponsor (Baxter Healthcare) will notify each doctor participating in the study. The doctor will be responsible for sharing this information with his/her patients.

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Informed Consent Information

The Food and Drug Administration (FDA), in cooperation with the National Institutes of Health (NIH), issued regulations (21 CFR 50.24) that will allow for certain emergency research to be conducted with an exception from informed consent. This change occurred in response to growing concerns that the former rules were making it impossible to carry out emergency care research at a time when the need for such research is increasingly recognized.

These 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 provide consent

-and the nature of the patient's life-threatening medical condition requires immediate treatment

-and there is evidence that the treatment to be tested has the potential to benefit the patient.

“Informed consent” is the process that allows a patient to decide, after understanding the risks and benefits of the research, whether he or she wants to voluntarily participate. An exception to this consent requirement is a serious matter and in response, the FDA and NIH have developed these regulations requiring additional protections for the patients eligible for these research protocols. 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. The additional protections include 1) consulting with the communities from which patients will be drawn 2) public disclosure of the study, 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 and 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 allow 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.

Informed Consent Procedures

The consent procedures followed in the protocol will follow the Federal Regulations set forth in 21 CFR 50.24 "Exception from informed consent requirements for emergency research". The Institutional Review Board (IRB) or ethics committee from each participating hospital has reviewed this study and has made sure that all of the rules are met and that they will be followed as the study goes on. Each IRB has found the following:

- The shock from blood loss suffered by patients eligible for this study is life-threatening and the current treatments are limited and need to be improved.
- The patients eligible for this study are not able to give

informed consent because they are in a severe shock state.

- Informed consent is not feasible before starting treatment with DCLHb because DCLHb must be given as soon as possible within minutes of the onset of the severe shock in order to increase the patient's chance of surviving.
- The patients eligible for this study cannot be identified before they are entered into the study because no one knows who will get hurt and end up in shock.
- The study is in the best interest of all severely injured trauma patients because their life-threatening injuries require immediate treatment and DCLHb may improve their treatment.
- Enough studies have been done with DCLHb to suggest that it may help trauma patients.
- The risks in giving DCLHb are reasonable given the condition of the trauma patients; that is, the chance of DCLHb helping severely ill shock patients is much greater than the chance DCLHb will further harm them.
- This study could not reasonably take place without an exception to the requirement for informed consent.
- An attempt will be made to contact a legally authorized representative for each patient within the window of time, if feasible, before the patient needs to be entered into the study.
- An informed consent document is available for obtaining consent from the patient or their legally authorized representative, if feasible.

Patients will not be compensated for their participation in the study.

- Any patients physically injured as a direct result of participation in this study will be provided the medical care needed to help them recover, at no cost to them, by the sponsor. No compensation other than free medical care will be provided.

[NIH: Waiver of Informed Consent Requirements in Certain
Emergency Research](#)

[FDA: Protection of Human Subjects; Informed Consent](#)

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