



October 10, 1997

2159 97 OCT 14 49:53

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 St. Anthony Hospital Central, Denver, CO; the University of Louisville Hospital, Louisville, KY; the University of Pittsburgh, Pittsburgh, PA; and the Pennsylvania State University, Hershey, PA.

The information from St. Anthony Hospital Central includes an outline of the April 3, 1997 Presentation to State Trauma Advisory Council (Attachment 1), an outline of the April 7, 1997 Presentation to Local Denver Business Leaders (Attachment 2), the April 7, 1997-advertisement that appeared in the Denver Post (Attachment 3), a copy of the flyer announcing the May 5, 1997 Hospital Presentation by Dr. Ed Sloan (Attachment 4) that was posted throughout the hospital, the electronic notification of May 5, 1997 presentation (Attachment 5) from Dr. Thomas Wachtel's office, an overview of Dr. Ed Sloan's May 5, 1997 presentation (Attachment 6), a copy of the slides for presentations to area trauma advisory councils (Foothills Area Trauma Advisory Council, Golden, CO; Central Rockies Area Trauma Advisory Council, Frisco, CO; Eastern Plains Area Trauma Advisory Council, Cheyenne Wells, CO; Pueblo Area Trauma Advisory Council, Pueblo, CO) (Attachment 7), and a Public Disclosure recap (Attachment 8). In accordance with 21 CFR §312.54, this information is also being submitted to the Docket Number 95S-0158 in the Dockets Management Branch.

95S-0158

SUP 12

Based on information received from the clinical site, the investigator and IRB achieved community consultation by holding meetings with the State Trauma Advisory Council, four (4) Area Trauma Advisory Councils, the Local Denver Business Leaders (Attachments 1 & 2), by holding a meeting open to the public where the study was presented (Attachment 6), and by printing advertisements that solicited communications from community members and provided information for contacting the principal investigator and the IRB (Attachment 3).

The information from the University of Louisville Hospital includes a study overview from Dr. Mallory titled, "University of Louisville DCLHb Study" and the HHS regulations 45 CFR §46 titled "Waiver of Informed Consent Requirements in Certain Emergency Research" (Attachment 9), model information for community consultation and public disclosure (Attachment 10), and a June 1, 1997 press release (Attachment 11). These documents were forwarded (the model information was forwarded only to physicians) to more than 20 key community members including representatives from the political arena including the Mayor's office, the County Judge, Louisville Board of Aldermen, Jefferson County Fiscal Court, the Lt. Governor's Office and Jefferson County Legislative Delegation; representatives from the educational arena including the University of Louisville Trustees, the UMC Board, the University of Louisville School of Medicine Dean's Office; and representatives from the community including the Jefferson County Medical Society, the Falls City Medical Society, the West Louisville Area Health Education System, Jefferson County Health Department, Interfaith Council of Louisville, African American Clergyman's Council, the Urban League, the Kentucky Cancer Program, Kentucky African-Americans Against Cancer, Kidney Disease Program, Minority Services, and other clergy and community leaders. The press release was also sent to an additional 200 people on the African Americans Against Cancer group mailing list and the American Cancer Society, Avon, Cancer Information Service, Falls City Medical Society, Family Health Center-Portland, Health Care Excel, James Graham Brown Cancer Center, Jefferson County Cooperative Extension, Jefferson County Health Department, Jefferson County Medical Society, Junior League of Louisville, Kentucky African Americans Against Cancer, Kentucky Cancer Program, Kentucky Cancer Registry, Kentucky Department for Public Health, Kentucky Homeplace Project, Park DuValle Community Health Center, University of Louisville Primary Care Center, University of Louisville Department of Radiology, West Louisville Area Health Education Center. Meetings were held with individuals and groups listed above as requested, as well as meetings with the Ethics Committee and Transfusion Committee. Also included for this site is a copy of the advertisement which included an 800 number for additional information or to comment on the research published in the following local newspapers: *The Courier Journal* (7 times), the *New Albany Tribune* (5 times), the *Jeffersonville Evening News* (5 times), the *Voice-Tribune* (3 times), the *Louisville Defender* (3 times), the *Southwest Newsweek* (3 times), and the *Louisville Eccentric Observer (LEO)* (3 times) (Attachment 12); articles published in the following local newspapers: July 14, 1997 *Lexington Herald-Leader, Lexington, KY*; July 30, 1997 *Louisville Courier Journal*; and July 31, 1997 *Lexington Herald-Leader, Lexington, KY* (Attachment 13); a copy of the article published in the July 18, 1997 *Inside U of L*; (Attachment 14); August 8, 1997, September 2, 1997 & September 8, 1997 correspondence

between the University of Louisville and the Jehovah's Witnesses organization (Attachment 15); and the transcript from August 13, 1997 local news show (Attachment 16). In accordance with 21 CFR §312.54, this information is also being submitted to the Docket Number 95S-0158 in the Dockets Management Branch.

Based on information received from the clinical site, the investigator and IRB achieved community consultation by contacting more than 20 key community members, followed by phone conversations and meetings with these individuals and groups, including contacts of the location Jehovah's Witness organization (Attachment 15); by printing advertisements in seven (7) local newspapers which included an 800 number to comment on the research (Attachment 12).

The information from the University of Pittsburgh includes the July 1, 1997 press release that was available on the University of Pittsburgh's Internet home page on July 2, 1997 @<http://www.upmc.edu/News/blood.htm> (Attachment 17); copies of two July 2, 1997 news releases published by *Dow Jones News Service* and *PR Newswire* (Attachment 18); an advertisement that was published in the following local newspapers on August 12, 1997: *Pittsburgh Post-Gazette*, *Tribune-Review*, *New Castle News*, *Greenville Record-Argus*, *Clarion News*, *Erie Daily Times*, and *The Vindicator* (Attachment 19); Read Ahead Material for May 5, 1997 Meeting (Attachment 20); a copy of the slides presented at the meeting with the City of Pittsburgh's Commission on Human Relations (16 member organization) (Attachment 21); and minutes from the meeting (Attachment 22). Also included is a transcript from a July 10, 1997 newscast about the study (Attachment 23). In accordance with 21 CFR §312.54, this information is also being submitted to the Docket Number 95S-0158 in the Dockets Management Branch.

Based on information received from the clinical site, the investigator and IRB achieved community consultation by contacting 16 members of the City of Pittsburgh's Commission on Human Relations and holding a meeting with the commission (Attachments 20-22); and by printing an advertisement in seven (7) local newspapers that included a telephone number established for soliciting communication from the public (Attachment 19).

The information from The Pennsylvania State University includes a summary of the first community consultation meeting attended by 12 key community members (Attachment 24); and a copy of a letter sent to other key community members representing the clergy, legal community, Jewish Community, African-American Community and Asian Community. Included with the letter was a summary of the study, the consent for insurance, the regulations compliance statement from the protocol (Attachment 25), and the radio transcript from "The Heart of the Matter" (Attachment 26); letters to the editors of two local newspapers: *Patriot News* and *Lebanon Daily News* (Attachment 27); a May 27, 1997 press release (Attachment 28); an article published in the local newspaper: *Patriot News* (Attachment 29); and an article published in the University's newspaper, the *Penn State Intercom* (Attachment 30), along with Penn State's Internet "Intercom

Online" publication. In accordance with 21 CFR §312.54, this information is also being submitted to the Docket Number 95S-0158 in the Dockets Management Branch.

Based on information received from the clinical site, the investigator and IRB achieved community consultation by holding a community consultation meeting (Attachment 24), mailing information and contacting representatives of the clergy, legal community, Jewish Community, African-American Community and Asian Community, and by presenting the study in three (3) local radio broadcasts including a phone number to call for additional information (Attachment 26).

The submission has been organized as follows:

St. Anthony Hospital Central

- Attachment 1: April 3, 1997 Presentation to Trauma Advisory Council
- Attachment 2: April 7, 1997 Presentation to Local Denver Business Leaders
- Attachment 3: April 7, 1997 advertisement (Denver Post)
- Attachment 4: Copy of Flyer for May 5, 1997 Meeting
- Attachment 5: Electronic Notification of May 5, 1997 Meeting
- Attachment 6: May 5, 1997 Meeting Overview
- Attachment 7: Slides from Presentations to 4 Area Trauma Advisory Councils
- Attachment 8: Public Disclosure Recap

University of Louisville Hospital

- Attachment 9: "University of Louisville DCLHb Study" Overview & HHS Regulations 45 CFR §46 titled "Waiver of Informed Consent Requirements in Certain Emergency Research"
- Attachment 10: Baxter's Model Information for Community Consultation and Public Disclosure
- Attachment 11: June 1, 1997 press release
- Attachment 12: Advertisement appearing in 7 local newspapers
- Attachment 13: 3 articles published in local newspapers
- Attachment 14: Article published in University of Louisville newspaper
- Attachment 15: Correspondence with the Jehovah's Witnesses Organization
- Attachment 16: August 13, 1997 local news show transcript

The University of Pittsburgh

- Attachment 17: July 1, 1997 press release
- Attachment 18: 2 July 2, 1997 news releases published by *Dow Jones News Service* and *PR Newswire*
- Attachment 19: August 12, 1997 advertisement printed in 7 local newspapers
- Attachment 20: Read Ahead Material for May 5, 1997 Meeting
- Attachment 21: Slides presented at the City of Pittsburgh's Commission on Human Relations meeting (May 5, 1997)
- Attachment 22: May 5, 1997 meeting minutes
- Attachment 23: July 10, 1997 newscast transcript

The Pennsylvania State University

- Attachment 24: Summary of first community consultation meeting with 12 key community members
- Attachment 25: Letter sent to other key community members
- Attachment 26: Radio transcript from "The Heart of the Matter"
- Attachment 27: Letters to the editors of two local newspapers
- Attachment 28: May 27, 1997 press release
- Attachment 29: Article published in a local newspaper
- Attachment 30: Article published in the University's newspaper and Penn State's Internet "Intercom Online" publication

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)270-5313.

Sincerely,



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

Presentation to State Trauma Advisory Council
Colorado Department of Health
Glendale, CO

April 3, 1997

DCLHb Traumatic Hemorrhagic Shock Study Overview

Inclusion/Exclusion Criteria

Study Endpoints

Exception From Informed Consent in Emergency Research
Use of exception in this study

Presentation to Local Denver Business Leaders
St. Anthony Hospital
Denver, CO

April 7, 1997

DCLHb Traumatic Hemorrhagic Shock Study Overview

Inclusion/Exclusion **C**riteria
Focus on patient **e**ligibility

Risks and Potential Benefits of the Product

Study Endpoints

Exception From Informed Consent in Emergency Research
Use of exception in this study

Patient Study Costs

Attachment 3

Try Us FREE!

never YOUR TIME links.

LIVE FREE TALK

Live

NI-5

FREE TV CALL

LINKLINE

LL FREE!

3-MEET

49¢

Legal Notices

Public Auction

Legal Notices

Legal Notices

Centura Health St. Anthony Hospital, a Level I trauma center, is participating in a research study for critically injured trauma patients admitted with severe loss of blood. These patients will receive an investigative hemoglobin solution in addition to the standard procedures for trauma care.

The Food and Drug Administration (Federal Register, Volume 61, pages 51498 to 51631) requires community consultation and public disclosure before initiating the study for the following reasons:

1. the research subjects will rarely be able to give their informed consent as a result of their medical condition;
2. the intervention involved in this research must be administered immediately often times before consent from the subject's legally authorized representative is feasible;
3. there is no reasonable way to identify in advance the individuals likely to become eligible for participation in the research.

Appropriate animal and 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 patients.

Anyone who has questions regarding this study may contact Thomas L. Wachtel, MD, principal investigator at 629-4222.



WORLD'S LARGEST Ford Expedition Dealer...

'97 FORD EXPEDITION

WORLD'S LARGEST EXPEDITION DEALER!

The All NEW '97 Ford Expedition

OVER 200 XLT & EDDIE BAUER EXPEDITIONS AVAILABLE

COURTESY FORD

8252 S. Broadway at G-470 738-4525

Legal Notices

1. All such claims shall be filed with the Authority for Claims, Institution, Department of Administration and the State Controller, State Services Building, Denver, Colorado.

2. Signature on the part of a creditor to file such final settlement will relieve the State of Colorado from any and all liability for such claim.

Dated at Denver, Colorado, this 7th day of March, 1997.

STATE OF COLORADO, each by and through the Authority for Claims, Institution, Department of Administration, Civil Rights and Administrative Services.

MEDIA OF PUBLICATION Daily Journal, Denver Post

PUBLICATION DATES: First March 31, 1997, Second April 7, 1997

Town of Parker, Colorado Public Works Department

Notice of Request for Proposal for Cottonwood Wetlands Re-seeding Project

The Town of Parker, Colorado is soliciting proposals for construction services to create a wetlands, wetlands restoration and new trail areas re-seeding to be located on Cherry Creek, approximately 3000 feet south of the Arapaho/Douglas County line at the Town's north border in Parker, CO 80134.

The construction services will include material, supplies, tools, labor, equipment and other services necessary for the construction and completion of the project described herein for the creation of the wetlands, restoration of the wetlands, and re-seeding operations.

CLIP AND SAVE

Find A Lawyer Fast, FREE & Easy!

Simply call 778-7100, mark the # below, and the Legal Specialty directory number of your choice.

DIRECTORY

- *910 Accident, Injury
- *920 Bankruptcy
- *925 Business & Financial Law
- *922 Child Support Collection
- *930 Civil Rights
- *915 Criminal Adult/Juvenile
- *924 Discrimination
- *935 Divorce & Custody
- *903 Drug Offenses
- *940 DUI/DWI
- *970 Employment Matters
- *904 Insurance Problems
- *985 IRS Tax Matters
- *917 Probate
- *975 Real Estate/Landlord/Tenant
- *916 Senior Citizen Matters
- *923 Sexual Harassment
- *980 Social Security/Disability
- *990 Traffic/DUI/DWI
- *999 Wills/Estate Planning
- *905 Workers Compensation

PLEASE POST

**TRAUMA SURGEON
DIVISION**

**MONDAY, MAY 5, 1997
BIRCH ROOM
6:00 P.M.**

GUEST SPEAKER:

Edward Sloan, M.D.

University of Illinois

Emergency Medicine - Research Division

PRESENTING:

Hemoglobin Therapy

***Dinner will be served
Please RSVP to Amy at 4-4222***

TO: Distribution list
FROM: SAC Trauma Service;4231 West 16th Avenue
SENT BY: Amy Sauer, Trauma Service
SUBJECT: May Trauma Surgeon Division Meeting & Guest Speaker
COPIES:

The next Trauma Surgeon Division meeting will be held Monday, May 5, 1997, at 6:00 p.m. in the Birch Room at St. Anthony Central. The guest speaker will be Dr. Edward Sloan, Department of Emergency Medicine, Research Division, University of Illinois.

Dr. Sloan will be presenting "Hemoglobin Therapy," and is the overall principle investigator in the study St. Anthony's is involved in re: Use of Diaspirin Cross-Linked Hemoglobin (DCLHb) for the Avoidance or Reduction of Perioperative Blood Transfusions.

Please plan on attending this informative presentation.

Overview of Trauma Surgeon Division presentation at St. Anthony's Hospital Central
May 5, 1997

General Greeting and Introductions- Thomas Wachtel, MD
Principal Investigator for THS study

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 PO₂, restores mucosal PO₂, 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 Trauma Surgeon Division presentation at St. Anthony's Hospital Central
May 5, 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**

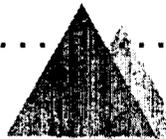


The Efficacy Trial of Diaspirin
Cross-Linked Hemoglobin
(DCLHb™) in the Treatment of
Severe Hemorrhagic Shock:

Baxter Healthcare Corporation
Protocol THS 95.1

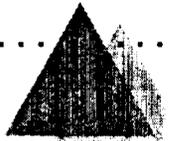
Investigators

- ◆ **Principal:** Thomas L. Wachtel, MD
- ◆ **Anesthesia:** Elliott Wohlner, MD
- ◆ **Emergency:** Peter Vellman, MD
- ◆ **Laboratory:** Chris Pizzo, MD
- ◆ **Trauma:** Jeffrey Cross, MD
- ◆ **Trauma:** Larry Rust, MD
- ◆ **Research:** Lee Hemminger, RN, MSN



Consent Form (I)

- ◆ **FDA 21 CFR 50.24**
- ◆ **Exception from informed consent requirements for emergency research.**
- ◆ **Lack of feasibility in obtaining informed consent in this patient population.**



Consent Form (II)

- ◆ **Favorable Risk/Benefit Profile.**
- ◆ **Informed Consent presented as soon as feasible for permission to continue the study.**
- ◆ **From the Patient, Legally Authorized Representative, or Family Member**



**Additional protections of the
rights and welfare of the patients.**

- ◆ **Community Consultation.**
 - ◆ **Public Notification *before* the Study.**
 - ◆ **Public Notification *after* Completion.**
- 

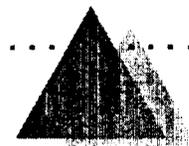
Additional protections of the rights and welfare of the patients.

◆ Community Consultation

- Decision to Conduct the Study**
- Exception to Informed Consent**
- Prior to Starting the Study**



Additional protections of the rights and welfare of the patients.

- ◆ **Public Notification *before* the Study.**
 - **Plans of the Investigation.**
 - **Risks and Benefits.**
 - **Prior to Starting the Study**
 - ◆ **Sponsor Submit Copies of Disclosed Information**
 - **IND File**
 - **Dockets Management Branch of FDA**
- 

Requirement to inform the public.

- ◆ **General Press Release?**
- ◆ **Public Hearing/Town Meeting?**
- ◆ **Radio/TV News Item?**
- ◆ **Newspaper Ad explaining the
Research Study?**

Additional protections of the rights and welfare of the patients.

- ◆ **Public Notification *after* Completion.**
 - **Demographic Characteristics of Research Population**
 - **Study Results**
- ◆ **Sponsor Submit Copies of Disclosed Information**
 - **IND File**
 - **Dockets Management Branch of FDA**

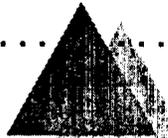
Patient Inclusion

- ◆ **Severe Injury resulting in Hemorrhagic Hypovolemic Shock, Tissue Hypoxia and Cellular Hypoperfusion:**
 - ▼ **Systolic BP <90 & P >120**
 - ▼ **Systolic BP <90 & P <60 + pre-terminal rhythm**
 - ▼ **Base deficit = 15 mmol/L or worse**
- ◆ **> 17 years**



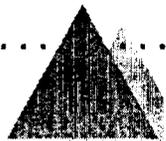
Patient Exclusion

- ◆ Hospitalization < 60 minutes
prior to start of infusion
- ◆ Known Injury Time < 4 hours
prior to start of infusion
- ◆ <18 years
- ◆ Pregnancy
- ◆ Isolated Head Injury



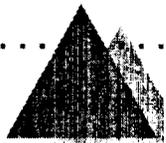
Patient Exclusion

- ◆ **Combined Multisystem and Head Trauma with Clinical Signs Consistent with Significant Mass Effect**
- ◆ **Pulseless traumatic arrest in hospital**
- ◆ **Imminent Death precluding resuscitative efforts**
- ◆ **Known Objection to the Use of Blood Products**



Method

- ◆ **Within 60 minutes of hospital arrival**
- ◆ **Random Assignment**
- ◆ **DCLHb or Normal Saline**
 - **500 ml initially**
 - ▼ **+(250 ml + 250 ml)**
 - ▼ **Within 60 minutes after first infusion**
- ◆ **Will receive all current modalities of treatment - blood/crystalloid/operation**



Method

- ◆ **Collect information**
 - **Vital Signs**
 - **Physical Examination**
 - **Laboratory**
 - ▼ **Urine**
 - ▼ **Venous Blood**
 - ▼ **Arterial Blood**

End Points

- ◆ **Primary**
- ◆ **Secondary**
- ◆ **Pharmacological**

End Points

- ◆ **Primary**
 - **28 Day Mortality Reduction**

End Points

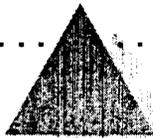
◆ Secondary

- **28 Day Morbidity Reduction**
 - ▼ Area Under the Curve (AUC) for
 - ▼ Multiple Organ Dysfunction (MOD) Score
- **48 Hour Mortality Reduction**
- **24 Hour Lactate Level Reduction**

End Points

◆ Pharmacological

- Blood Utilization Reduction
- Ventilator Reduction
- ICU Reduction
- Dialysis Reduction
- Total Hospital Day Reduction

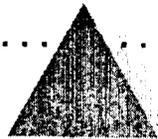


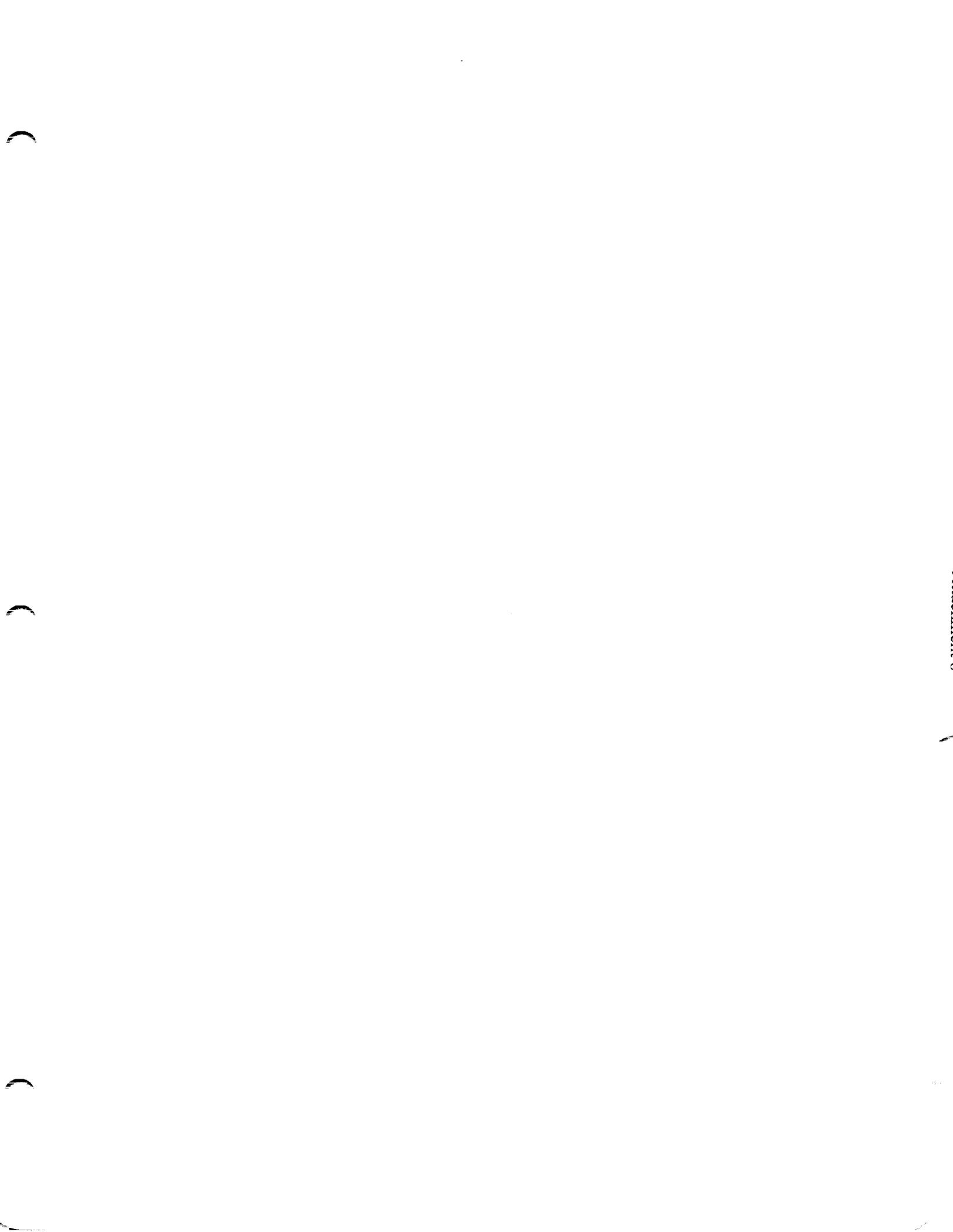
Known Patient Benefits

◆ None

Possible Benefits from Animal Studies

- ◆ Increases mean arterial pressure
- ◆ Transports Oxygen *in vivo*
- ◆ Optimizes Vital Organ Blood Flow
- ◆ Prevents Early Tissue Hypoxia
- ◆ Prevents Lactic Acidosis
- ◆ Improves Survival





ST. ANTHONY HOSPITAL CENTRAL

PUBLIC DISCLOSURE RECAP

1. LOCAL BUSINESS LEADERS, April 7, 1997. Under the auspice of St. Anthony Foundation, approximately 30 local business men toured the hospital, and were advised of current and future planned research projects. There were no particular questions regarding the DCLHb study, and the general consensus was approval of our efforts to advance the science of medicine.

2. TRAUMA SURGEONS NOTIFICATION, May 5, 1997. At a regular monthly meeting, Dr. Ed Sloan, Principal Investigator from Cook County Hospital, Chicago, made a formal presentation to all the trauma surgeons. Main questions related to ability to continue each physicians' standard of care for patients enrolled into study. Dr. Sloan satisfactorily answered these questions, and there was a general sense of enthusiasm among the surgeons to begin the study.

3. INFORMATION TO THE COLORADO STATE WIDE TRAUMA ADVISORY COUNCILS:
Dr. Wachtel presented the study to each of the following advisory councils:

April 3, 1997 - State Trauma Advisory Council, Colorado Department of Health, Glendale, Co.

May 7, 1997 - Foothills Area Trauma Advisory Council (ATAC), Golden, Colorado

May 8, 1997 - Central Rockies Area Trauma Advisory Council, Frisco, Colorado

June 11, 1997 - Eastern Plains Area Trauma Advisory Council, Cheyenne Wells, Colorado

July 8, 1997 - Pueblo Area Trauma Advisory Council, Pueblo, Colorado

Dr. Wachtel reports that the study concept was well received, with few questions. The main question was how it would affect the current referral system, and if there was anything the outlying facilities needed to do to facilitate the study. The study will not affect referral patterns.

4. CENTURA HEALTH TRAUMA SYSTEM: May 14, 1997. A meeting was held at the central Centura offices, Denver Tech Center, Englewood, Colorado 80011, with trauma personnel from all the Centura hospitals in the state of Colorado. At that time, Dr. Wachtel again presented the DCLHb protocol. He states there were no questions, but general support for the project.

UNIVERSITY OF LOUISVILLE DCLHb STUDY

Blood product may save lives

University of Louisville Hospital is among 35 major trauma centers that are evaluating a new treatment for critically injured patients with severe blood loss. The treatment involves administering an experimental blood product to such patients, who face a major risk of dying despite the best medical care. Baxter Healthcare, Inc., has developed the product, Diaspirin Cross-linked Hemoglobin (DCLHb). Which is being tested during the emergency treatment of trauma patients in shock. The trial, which is authorized by the U.S. Food and Drug Administration, requires public notice because it will occur under emergency conditions that may require an exception from informed consent. This notice attempts to address questions about the trial.

Q. Why is this trial being performed?

A. Seriously injured patients frequently arrive at the hospital in shock with significant blood loss. Despite the best care medicine has to offer, as many as 40% of the most critically injured patients will die from their injuries. Studies suggest that DCLHb may improve the chance of survival following severe blood loss. The product has the greatest chance of improving survival and reducing complications when it is given immediately after the beginning of catastrophic shock and bleeding.

Q. What is DCLHb?

A. DCLHb is a purified hemoglobin (the part of blood that carries oxygen) preparation made from human blood that has become outdated on blood bank shelves and is no longer usable for transfusions. It is filtered and heated to reduce the risk of blood-borne infections including AIDS. DCLHb may restore blood pressure, increase blood flow to vital organs and carry oxygen to cells and tissues. Because blood typing is not required and the product can be stored in the Emergency Department, DCLHb can be given immediately after a patient's arrival, saving critical moments in stabilizing a trauma patient.

Q. Does DCLHb replace the need for blood transfusion?

A. DCLHb is administered in addition to transfusions that may be needed to treat the injured patient. (Since the product is made from human blood, it would may not be suitable in treating patients whose religious beliefs forbid blood transfusions.) All patients will still get all standard therapies in this study, including blood, fluids and surgery. Although DCLHb may someday reduce the number of blood transfusions required to treat the injured, volunteer blood donations are still vital.

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

A. Because trauma patients in this study are so severely injured, they will not be able to give their consent to participate. They are in critical need of immediate lifesaving treatment. The U.S. Food and Drug Administration has granted an exception from informed consent in such cases. They have carefully evaluated DCLHb 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 legal representatives, or family before DCLHb is given. Unfortunately legal representatives may not be immediately available. All patients and their 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. There are no known risks to patients who decide not to **continue in the study**.

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

A. DCLHb has been extensively studied in randomized trials involving more than 700 patients over a four-year period to evaluate its effects. Of the approximately 350 who received the drug, a few temporary side effects were noted. These included changes in some lab test results, a temporary and harmless yellowing of the skin (unrelated to liver damage), temporary reddening of the urine due to the red color of DCLHb, nausea, and back, abdominal and muscle pain. Blood pressure may be elevated following administration; however, this may be beneficial to patients in shock, whose blood pressure is dangerously low. Independent experts will

monitor patient safety throughout the trial. The University of Louisville is participating in this drug trial because the benefits to severely injured trauma patients may greatly exceed known side effects of the treatment.

Q. Who will be eligible to participate?

A. Approximately 25-30 patients with low blood pressure and in shock from blood loss following traumatic injury will be enrolled at U of L over the next 18 months. Approximately half of these patients will receive the blood product along with other treatment. This product will be given only to patients who have such major blood loss that standard therapy may not be enough to save their lives. A total of 850 patients will be enrolled nationwide at 35 trauma centers. This trial is being performed under the guidelines and approval of the Institutional Review Board of the University of Louisville, and the U.S. Food and Drug Administration. No additional charges will be incurred by patient as a result of participation.

We at the University of Louisville are excited about the potential that products such as DCLHb may have to not only save lives. But also to extend the useful life of a very scarce resource- human blood supplies. This product is an example of how research can expand the safety net, and it is another example of why blood donations are critical to help save lives.

Mary Nan S. Mallory, MD
Assistant Professor
Department of Emergency Medicine
University of Louisville

852-5689

notifies the sponsor that an application is required for an investigation.

(4)(i) A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization of FDA. FDA shall provide such written authorization 30 days after FDA receives the IDE or earlier.

(ii) If the investigation involves an exception from informed consent under § 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in § 50.24 of this chapter.

20. Section 812.35 is amended by adding a new sentence to the end of paragraph (a) to read as follows:

§ 812.35 Supplemental applications.

(a) * * * Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in § 50.24 of this chapter, the sponsor shall submit a separate IDE for such investigation.

21. Section 812.36 is amended by adding a new paragraph (b)(4) to read as follows:

§ 812.36 Confidentiality of data and information.

(b) * * *

(4) Notwithstanding paragraph (b)(2) of this section, FDA will make available to the public, upon request, the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

22. New section 812.47 is added to subpart C to read as follows:

§ 812.47 Emergency research under § 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under § 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures under § 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor

shall promptly submit to the IDE file and to Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, copies of the information that was disclosed, identified by the IDE number.

(b) The sponsor also shall monitor such investigations to determine when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA investigators who are asked to participate in this or a substantially equivalent clinical investigation and other IRB's that are asked to review this or a substantially equivalent investigation.

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

23. The authority citation for 21 CFR part 814 is revised to read as follows:

Authority: Secs. 501, 502, 503, 510, 513-520, 701, 702, 703, 704, 705, 706, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 352, 353, 360, 360c-360j, 371, 372, 373, 374, 375, 376, 379a, 381).

24. Section 814.9 is amended by redesignating paragraph (d) as paragraph (d)(1) and by adding new paragraph (d)(2) to read as follows:

§ 814.9 Confidentiality of data and information in a premarket application (PMA) file.

(d)(1) * * *

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

Dated: July 17, 1996.

David A. Kessler,
Commissioner of Food and Drugs.

Dona E. Shalala,
Secretary of Health and Human Services.
[FR Doc. 96-24967 Filed 9-26-96; 8:59 am]
BILLING CODE 4120-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

45 CFR Part 46

Waiver of Informed Consent Requirements in Certain Emergency Research

AGENCY: National Institutes of Health, HHS.

ACTION: Waiver.

SUMMARY: The Department of Health and Human Services (HHS) is announcing the waiver of the applicability of the title 45 CFR part 46 (protection of human subjects) requirement for obtaining and documenting informed consent, for a strictly limited class of research involving activities which may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. However, because of special regulatory limitations relating to research involving prisoners (subpart C of 45 CFR part 46) and research involving fetuses, pregnant women, and human in vitro fertilization (subpart B of 45 CFR part 46), this waiver is inapplicable to these categories of research.

EFFECTIVE DATE: November 1, 1996.

FOR FURTHER INFORMATION CONTACT: F. William Dammol, Jr., J.D. Senior Policy Advisor, Office for Protection from Research Risks, 6100 Executive Boulevard, Suite 3B01, National Institutes of Health, MSC 7507, Rockville, MD 20892-7507. Telephone (301) 496-7005, ext. 203 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Waiver

Pursuant to Section 46.101(i) of title 45 of the Code of Federal Regulations, the Secretary of Health and Human Services (HHS) has waived the general requirements for informed consent at 45 CFR 46.115 (a) and (b), and at 46.408, (to be referred to as the "Emergency Research Consent Waiver," for a class of research consisting of activities¹, each of which have met the following strictly limited conditions detailed under either (a) or (b) below:

¹ Because of special regulatory limitations relating to research involving prisoners (subpart C of 45 CFR part 46), and research involving fetuses, pregnant women, and human in vitro fertilization (subpart B of 45 CFR part 46), this waiver is inapplicable to these categories of research.

(r) The Institutional Review Board (IRB) responsible for the review, approval, and continuing review of the research activity has approved both the activity and a waiver of informed consent and found and documented:

(1) that the research activity is subject to regulations codified by the Food and Drug Administration (FDA) at Title 21 CFR part 50 and will be carried out under an FDA investigational new drug application (IND) or an FDA investigational device exemption (IDE), the application for which has clearly identified the protocols that would include subjects who are unable to consent, and

(2) that the requirements for exception from informed consent for emergency research detailed in title 21 CFR section 50.24 have been met relative to those protocols, or

(b) The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has found and documented that the research is not subject to regulations codified by the FDA at title 21 CFR part 50 and found and documented and reported to the Office for Protection from Research Risks, Department of Health and Human Services, that the following conditions have been met relative to the research:

(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 involved in the research 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 research.

(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) The risks associated with the research 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 research could not practicably be carried out without the waiver.

(5) The proposed research protocol 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 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 in accord with Sections 46.116 and 46.117 of title 45 of the Code of Federal Regulations. 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 research consistent with paragraph (b)(7)(v) of this waiver.

(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 research will be conducted and from which the subjects will be drawn;

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

(iii) Public disclosure of sufficient information following completion of the research 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 research; 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 contact within the therapeutic window the subject's family member who is not a legally authorized representative, asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

In addition, 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 legal authorized representative of the subject or if such a representative is not reasonably available, a family member of the subject's inclusion in the research, the details of the research 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 subject remains incapacitated, a legal 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 family member is told about the research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

For the purposes of this waiver "family member" means any one of the following legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and an individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

Background

It had come to the attention of HHS that there are proposals to conduct certain research, including National Institutes of Health (NIH) funded research, which could not go forward

Federal Register / Vol. 61, No. 192 / Wednesday, October 2, 1996 / Rules and Regulations 5153

the context of the current HHS regulations for the protection of human subjects (45 CFR part 46), unless certain informed consent requirements of those regulations were waived in accord with the waiver provisions provided at 45 CFR 46.101(i). HHS carefully reviewed the need for the exercise of the Section 46.101(i) waiver authority in these circumstances, and the requirements for informed consent were waived by the Secretary in the instance of only one specific multi-site study of head injuries which is currently underway (60 FR 38353).

The Secretary is now waiving the informed consent requirements for the class of research activities and no longer restricting the waiver to a single research project. This waiver provides clear instruction as to when research in emergency circumstances may proceed without obtaining an individual subject's informed consent. Elsewhere in this edition of the Federal Register, the FDA is publishing a final rule which amends FDA regulations to authorize a nearly identical waiver of informed consent in research which is regulated by FDA. The joint publication of these actions permit harmonization of the HHS and FDA regulations regarding

research in emergency circumstances. The HHS waiver, just as the FDA regulatory change, provides a narrow exception to the requirement for obtaining and documenting informed consent from each human subject or his or her legally authorized representative prior to initiation of research if the waiver of informed consent is approved by an IRB. The waiver authorization applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition, and who do not have available a legally authorized person to represent them. The Secretary, HHS is authorizing this waiver in response to growing concerns that current regulations, absent this waiver, are making high quality research in emergency circumstances difficult or impossible to carry out at a time when the need for such research is increasingly recognized.

HHS notes testimonies to this effect delivered to (i) the Subcommittee on Regulation, Business Opportunities, and Technology, Committee on Small Business, U.S. House of Representatives (Washington DC, May 23, 1994); (ii) the

Coalition Conference of Acute Resuscitation Researchers (Washington DC, October 25, 1994); (iii) the meeting of Applied Research Ethics National Association (Boston MA, October 30, 1994); (iv) the meeting of Public Responsibility in Medicine & Research (Boston MA, November 1, 1994); and (v) the Food and Drug Administration/ National Institutes of Health Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances (Rockville MD, January 9-10, 1995).

Periodic Review

A periodic review of the implementation by IRBs of this Section 101(i) waiver will be conducted by the Office for Protection from Research Risks, National Institutes of Health, to determine the adequacy of the waiver in meeting its intended need or if adjustments to the waiver might be necessary and appropriate.

Dated: July 17, 1996.

Donna E. Shalala,

Secretary.

[FR Doc. 96-24968 Filed 9-26-96; 8:59 am]

BILLING CODE 4160-04-M

Baxter Healthcare Corporation

Model Information for Use in Community Consultation and Public Disclosure

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

*The information in this document is provided in accordance with the U.S. Food and Drug Administration (FDA) regulation, effective November 1, 1996: “Exception from informed consent requirements for emergency research” (21 CFR 50.24). This information is provided to aid in informing the **public** about the nature of this trauma study, including the risks and potential benefits to patients.*

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 due to trauma injuries. **Many others suffer** from prolonged illness. Advancements in trauma care are necessary in order to make **more likely** the survival and complete recovery of people suffering from severe traumatic injuries.

Study Introduction

Patients who have **experienced** a severe traumatic injury often suffer from shock due to excessive blood loss. Shock means the body is unable to deliver enough blood and oxygen to all of the vital organs and tissues. When this happens, vital organs may no longer be able to function correctly and death may occur as a result. This shock cannot always be cured by medical treatments now available. The current medical treatment often involves the rapid infusion of large volumes of different liquids such as saline (salt water) and the transfusion of blood, to **replace the fluid and blood loss**. Immediate surgery is often needed to repair the injuries.

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 unpredictable**, a legally authorized representative is usually not available to provide consent for the patient and contacting a family member is often not possible. An exception from consent will be utilized when obtaining prospective informed consent from the patient or their legally authorized representative is not feasible, due to the critically short time in which the patient must be treated and DCLHb infused.

DCLHb Background

Diaspirin Cross-Linked Hemoglobin (DCLHb) is a purified human hemoglobin solution. Hemoglobin is the protein in red blood cells that carries oxygen. The product is prepared from units of human red blood cells from volunteer donors which have been

tested and found negative for the viruses that cause hepatitis and AIDS. Also, the DCLHb is heated and filtered during the manufacturing process. These processes add extra steps to make the solution safe from viruses.

DCLHb can be given immediately to a patient of any blood type. It does not need to be cross-matched which must be done before giving blood. It can be easily stored in the emergency department of the hospital so that it is available as soon as a patient arrives. DCLHb carries oxygen and may improve oxygen delivery to the organs that need oxygen the most. The delivery of oxygen to vital organs may reverse the destructive effects of shock, and may allow for increased survival and complete recovery of more patients who are severely injured.

Informed Consent Background

The FDA, in cooperation with NIH, issued regulations that will allow for certain emergency research to be conducted with an exception from informed consent 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 patients medical condition requires immediate treatment.

Informed consent is the process which allows a patient to decide, after understanding the risks and benefits of the research, whether or not 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 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 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.

DCLHb Preclinical Information

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 may be 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.

DCLHb Clinical Information

In the over 700 patients who have participated in DCLHb studies to date, more than 350 have received DCLHb. The clinical studies have involved 26 hospitals or universities in the U.S. and 8 other countries. During the 5 years of human clinical work, 12 studies have been completed and 4 are currently underway. DCLHb is or 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.

Allergic, renal, pulmonary, cardiac, neurologic, or infectious complications have not been consistently seen with DCLHb use. Some laboratory tests have been noted to change with DCLHb use, including proteins and enzymes that could indicate damage to organs such as the pancreas and liver, or to muscles. In patients who have received doses of DCLHb greater than 500 mL, blood amylase (an enzyme of the pancreas, a digestive organ) and jaundice (yellow coloring of the skin) have been seen. The jaundice starts soon after DCLHb infusion and usually lasts approximately three days without the occurrence of any medical problems. Inflammation of the pancreas, or pancreatitis, has been seen in four patients (two reported as serious and related to DCLHb) who received DCLHb and two patients who did not receive DCLHb in these studies.

The initial clinical trial of DCLHb 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 approximately 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 DCLHb's safety and effectiveness in preventing blood transfusions. DCLHb is also going to be tested in a prehospital trial of hemorrhagic shock in trauma patients in Europe.

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 is to begin giving 500 mLs (1 pint) to 1000 mLs (2 pints) of DLCHb 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.

Study Design

In this trial, the patients will be randomly (like a flip of the coin) assigned to receive either the 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 the 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 or not there is a decrease in 28 day mortality 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 or not 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 byproduct of shock caused by a lack of oxygen being delivered to tissues and cells.
- This study is designed to determine whether or not there is a decrease in 48 hour mortality 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.

The 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 ($\frac{1}{2}$ 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 for this Study

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 IRB from the hospital giving this presentation 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. The IRB has found the following:

- The shock from blood loss suffered by patients eligible for this study are in 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 informed consent.
- An attempt will be made to contact a legally authorized representative for each patient within the window of time before the patient needs to be entered into the study, if feasible.
- An informed consent document is available for obtaining consent from the patient or their legally authorized representative, if feasible.
- If the patient or their legally authorized representative is not available, an attempt will be made to contact a family member of the patient's within the window of time before the patient needs to be entered into the study, if feasible.
- Information is available to provide to a family member of the patient and the family member will be able to refuse to allow the patient to be included in the study.

•If consent is not feasible during the therapeutic window, the patient, their legally authorized representative, or their family member will be notified of the study, as soon as feasible, and may refuse to continue participation in the study for any reason, at any time without any penalty. The patient's medical care will not be affected by their decision, nor will they lose any benefits they might otherwise receive.

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 DLCHb could cause reactions or discomforts that were seen in previously completed animal and/or human studies with various hemoglobin solutions. Possible reactions that may occur from infusion with DCLHb are:

- stomach pain (gas, bloating), stomach cramps, constipation, nausea or vomiting shortly after infusions
- back pain or muscle aches
- temporary general weakness or discomfort, headache
- a red discoloration of urine caused by hemoglobin (the protein found in red blood cells that carries oxygen)
- 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
- temporary inability to do certain laboratory tests accurately
- temporary rise in blood pressure requiring treatment
- temporary jaundice-like condition (yellow skin)
- abnormal kidney function
- temporary increase in the time it takes for blood to clot
- small areas of damage in heart muscle, liver, or kidneys (only seen in some laboratory animals)
- allergic reactions such as chills, elevated temperature, or skin rash

DCLHb has been studied in over 350 patients, thus far, including patients with conditions other than severe traumatic shock, including 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 may be 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 currently unknown.

Also, patients with severe trauma are currently being 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 may 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.

Voluntary Continued Participation and Withdrawal

If consent from the patient or their legally authorized representative is feasible, the decision to participate will be voluntary. If informed consent is not feasible, an attempt will be made to inform a family member. The family member's decision to include the patient in the study will be voluntary. Even if the decision is made for the patient to take part in the study, the patient may be withdrawn from the study at any time. The patient's medical care will not be affected by this decision, nor will the patient lose any benefits he or she might otherwise receive.

In addition, if consent is not feasible during the time in which DCLHb must be given, the patient, their legally authorized representative, or their family member will be notified of the study, as soon as feasible. Any of these parties may refuse to the continued participation of the patient in the study for any reason, at any time without any penalty. The patient's medical care will not be affected by their decision, nor will they lose any benefits they might otherwise receive. If a patient decides to withdraw from the study, all data collected from that patient will be used up to the time he or she withdrew. This information is necessary in determining the safety and efficacy of the product and is mandated by the FDA. Any patient who decides to withdraw, or declines to continue participation in the study, will be asked to consent to a 28 day follow-up contact which may be made by phone. Once a patient has declined to participate further in the study, no other contact will be made with the patient unless a safety issue arises that requires further contact. Information that is part of public record may be used.

A patient's doctor may withdraw them from a study at any time without their consent if they believe that withdrawal is in the patient's best interest. The study sponsor or the FDA may also cancel this study at anytime.

Confidentiality

A patient's participation in this study will remain confidential. To make sure the information from this study is accurate, the study sponsor (Baxter Healthcare), their representatives (ClinTrials Research or other auditors), the Institutional Review Board, the FDA, and other governmental agencies, may inspect the records concerning a patient's participation in this study. Information gathered from this study may be submitted to governmental or regulatory agencies in other countries where the study drug may be considered for approval. No patients will be identified by name as a result of any audit or in any publication of information from this study.

Compensation for Research-Related Injury

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.

Contact for Further Information

For any questions regarding this study, or patient's rights, please contact the doctor responsible for the study at this clinical site.



press release

June 1, 1997

FOR IMMEDIATE RELEASE

Randi Hansen

Ken Marshall

U of L MEDICAL SCHOOL HOSPITAL TO STUDY NEW
BLOOD-BASED MEDICATION FOR TRAUMA CARE

LOUISVILLE, Ky. — A newly developed product that may allow emergency physicians to more quickly treat trauma patients who have suffered severe blood loss will be studied at U of L Hospital by emergency medicine and trauma surgeon researchers at the University of Louisville. The study of Diasprin Cross-Linked Hemoglobin (DCLHb) is set to begin later this month.

U of L Hospital will become the first hospital in Kentucky to use the hemoglobin-based product to treat approximately 20-30 trauma patients. Study criteria dictate that only the most seriously injured patients who have severe shock and bleeding have the opportunity to be enrolled. These patients are at the greatest risk of death.

All patients will continue to receive the best possible medical care currently available. The DCLHb treatment will be administered as additional therapy. The study is nationally randomized; of those patients who fit the treatment parameters, approximately half will receive this additional treatment step, the other half will not.

U of L has been authorized by the U.S. Food and Drug Administration to study the product in its trauma center during a two-year clinical trial. U of L and federal research protocols dictate that a patient must give informed consent before being enrolled in any clinical trial. However, patients who have suffered severe trauma and loss of blood — the type of case for which U of L's DCLHb study was designed — are sometimes not physically able to give informed consent, nor can next of kin be located in time to administer treatment.

In such cases, U of L will utilize a waiver of informed consent recently authorized by the FDA for just such contingencies. The waiver allows U of L researchers at U of L Hospital to administer DCLHb even before informed consent can be given. The study was reviewed and approved by a U of L committee that oversees the protection of human subjects in research. Patients and their families, however, have the right to withdraw from the trial at any time after they have been informed.

DCLHb is prepared from chemically modified human red blood cells. The product is sterilized and pasteurized, and can be frozen for up to one year. Most importantly, it does not require a cross match with the patient's own blood and can be used on anyone.

"Diasprin holds great promise for our patients with severe traumatic injury," said Mary Nan Mallory, principal investigator for the Kentucky DCLHb study, and a physician in U of L's emergency medicine department. During severe blood loss, Mallory explained, a patient's 28-day mortality rate increases because of damage to internal organs and tissues. "This study," she added, "is designed to determine if the use of DCLHb can decrease the number of deaths that occur in that 28-day window."

U of L Hospital is a Level I Trauma Center and one of 35 U.S. sites to be involved in the clinical trial of DCLHb. The product, manufactured by Baxter Healthcare Corp. in Deerfield, Ill., already has been tested extensively in the U.S. and abroad as a treatment for trauma, stroke, kidney dialysis, overwhelming infection, critical ICU illness and acute anemia, as well as in surgery to reduce the need for blood transfusions.

A special telephone number, 1-800-⁷⁶³⁻⁴⁹¹⁶~~xxx-xxxx~~, has been set up to allow community members to comment and/or submit questions. Callers who have questions can leave a message, including their telephone numbers, and a study staff member will answer such questions by return phone call. A mechanism also is available to exclude from the study those who wish.

For more information, contact Randi Hansen at the University of Louisville School of Medicine, (502) 852-7104, or Ken Marshall at U of L Hospital, (502) 562-4007.

###



Relatives of John William Hall and Eva Lomas Reunion. July 20, 1 p.m., at the home of Mae McCarty, Taylorsville, Ky. Potluck meal. Information: Mae Sparrow McCarty, (502) 477-1706, or Betty Hall



Stuart High School Class of 1970

Aug. 9. Information: Mona, (502) 239-4476.

Vicco High School Alumni and Friends Association. Aug. 16, noon, Eastern Kentucky University, Faculty Alumni Center, Arlington Mule Barn, Richmond, Ky. Information: Don Kelly, (502) 245-5963.

Descendants of John and James Reuchle. Aug. 16, Breckinridge Inn. Information: Lucille Jenkins, 1305 Witawanga Ave., Louisville, Ky. 40222; (502) 425-7168.

DuPont Manual Class of 1956. Oct. 25, Executive West Hotel. Information: Dale Vassie, (502) 634-1145.

Listings appear each Sunday. Items must be submitted in writing and be received by the Courier-Journal Listings Bureau, P.O. Box 740031, Louisville, Ky. 40201-7431, no later than noon Thursday.

An important message from the University of Louisville School of Medicine and U of L Hospital

After a decade of scientific research, ample evidence exists that a blood product known as **Diasprin Cross-Linked Hemoglobin (DCLHb)** may have lifesaving potential for severely injured patients.

The U of L School of Medicine's emergency medicine and surgery departments at U of L Hospital has been chosen by DCLHb's manufacturer, Baxter Healthcare Corp. of Deerfield, IL, as one of 35 centers nationwide to test DCLHb's effectiveness in treating life-threatening blood loss that occurs from severe traumatic injury. Just 20-30 Louisville-area patients will have the opportunity to participate in this nationally randomized study. Research criteria dictate that **only the most seriously injured patients who have severe shock and bleeding will be eligible.** These patients have the greatest risk for death.

U of L and federal research protocols dictate that a patient must give informed consent before being enrolled in any clinical medication trial. However, many of the patients eligible for this study may not be physically able to give informed consent, nor can next of kin always be found in time to administer treatment.

In such cases, U of L will utilize a waiver of informed consent recently authorized by the FDA for just such contingencies. The waiver allows U of L researchers at U of L Hospital to administer DCLHb even before informed consent can be given. Patients and their families, however, have the right to withdraw from the trial at any time after they have been informed.

If you are interested in finding out more about this study or would like to comment, please call the University of Louisville emergency medicine department at 1-800-763-4916. Our physicians will be happy to answer your questions.

UofL Health Sciences Center

UNIVERSITY MEDICAL CENTER, INC.™

This message is provided in accordance with the U.S. Dept. of Health and Human Services regulation, effective October 2, 1996: "Exception from informed consent requirements in certain emergency research" (45 CFR Part 46).

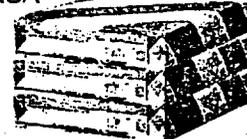
233MHz Pentium® Processor
With MMX™ Technology

****14" (12.9" viewable) 26mm Color Monitor**

Limited to stock on hand. No phone orders. While supplies last. registered trademarks and MMX is a trademark of Intel Corpor.

BUY 3 REAMS GET 1 REAM FREE!

XEROX



Premium Copy Paper

- 20 lb. white paper, 83 brightness
- 500 sheets of 8-1/2" x 11"

\$3.39

Per ream

List Price \$9.60

0600-0560

*Limit 2 offers per customer.

OfficeMax Everyday Low Price

2-SPEED MOTOR

7" Personal Desk Fan

- 3-position switch
- Air flow tilt adjustment

List Price \$19.99

1201-3787

\$12.99

OfficeMax Everyday Low Price

NO PAYMENTS NO INTEREST

Until January '98 on in-store purchases of \$299 or more.

purchases of computers, business machines, and furniture available to purchases made on the OfficeMax Business

FREE Delivery! Call:

Store Hours: 9

©OMX, Inc. We reserve the right to limit

1

2

3

4

5

akeover
unching"
en content

LOCAL NEWS

LEXINGTON HERALD-LEADER

MONDAY
July 14, 1997
Lexington, Ky.



SECTION
Classifieds
Crossword
Obituaries
Short Takes

B:
B:
B:
B:

U of L joins blood substitute search

UK program testing different method

BY JIM WARREN

HERALD-LEADER MEDICAL WRITER

Another Kentucky hospital is plunging into the potentially exciting new world of artificial blood.

Doctors at the University of Louisville Hospital say they'll start giving an experimental new blood substitute to selected trauma patients later this month. It's part of a

two-year national study to evaluate the hemoglobin-based product in patients suffering from severe blood loss.

Blood loss kills up to 40 percent of patients with severe traumatic injuries. Even patients who survive initial blood loss remain at risk of death for up to a month because of damage to internal organs and tis-

sues. Part of the test is to determine whether the substitute blood can reduce deaths during this period, officials said.

The University of Kentucky Hospital began testing a different type of blood substitute this spring in patients undergoing heart bypass surgery. The material UK is using, made by Somatogen Inc. of California, is produced artificially by genetically engineered bacteria.

U of L is testing Diasprin Cross-

Linked Hemoglobin, which is processed from human blood that has been stored in blood banks so long it is "outdated." It's made by Illinois-based Baxter Healthcare Corp.

Dr. Mary Nan Mallory, an associate professor of emergency medicine at U of L and principal investigator on the study, said 20 to 30 trauma patients who have lost large amounts of blood will be given the blood substitute, along with transfu-

sions of "real" blood. Only injury patients who are at high risk of death from shock and blood loss will be enrolled in the study, she said.

Several competing blood substitutes now are being evaluated at medical centers nationwide.

All blood substitutes basically consist of hemoglobin — the protein in red blood cells that carry life-giving oxygen. No one has tried to de-

SEE BLOOD, B3

BLOOD: Search on for substitute

FROM PAGE B1

velop a substitute for whole blood, which is thought to be too complex to duplicate.

FDA approval of blood substitutes for general use probably is four or five years away. But biotechnical and pharmaceutical companies are trying to get blood substitutes into the testing stage now in hopes of cashing in on what could be a \$25 billion-a-year market.

Diasprin Cross-Linked Hemoglobin has been given to about 700 patients nationwide in early trials with a few temporary side effects, according to U of L. These included temporary but harmless yellowing of the skin, temporary reddening of the urine, nausea and some back pain.

While patients will be monitored for any problems, Mallory said the blood substitute's side effects should be more than offset by these advantages:

- The product can be given to anyone, regardless of blood type. No blood typing is necessary, saving valuable time in the emergency room.

- Fewer blood transfusions would be needed, allowing more efficient use of blood supplies.

- The blood substitute is sterilized, eliminating any risk of spread-

ing AIDS, hepatitis or other blood-borne illnesses.

According to Mallory, U of L will offer the blood substitute only to patients who arrive at the hospital in life-threatening shock from blood loss after traumatic injury. Half the patients will receive the blood substitute along with traditional treatments, and half will receive traditional treatments alone.

Doctors will secure patients' consent before giving the blood substitute. But in cases where a patient is physically unable to give consent, U of L will use a waiver of consent authorized by the FDA for such situations. Patients or their families can drop out of the study any time.

According to Mallory, U of L Hospital is one of about 40 medical centers nationwide that will test Diasprin Cross-Linked Hemoglobin over the next two years. A total of about 850 patients will receive the blood substitute over the course of the trial, she said.

Because of the unusual nature of the study, U of L has set up a special phone number that people can call to submit questions or comments. Callers can leave messages, along with their phone numbers, and U of L staffers will call them back. They also can ask to be excluded from the study. The number is (800) 763-4916.

U of L to test product that may save people who lose a lot of blood

It could restore blood pressure, flow to vital organs

By DICK KALIKAS
The Courier-Journal

Emergency room doctors at the University of Louisville are about to start testing a new product that they hope will increase the survival rate of patients who have lost a lot of blood.

Preliminary studies have shown that Diasprin Cross-Linked Hemoglo-

bin has promise for restoring blood pressure and circulation to people who have lost about half of their blood from trauma.

Almost half of patients with severe blood loss die within 28 days of their injury, in large part because of damage to vital organs caused by lack of oxygen, which is carried by the blood.

The new product is made from outdated human blood stored in blood banks. The blood is filtered, heated and undergoes other treatment. The result is a product that can be used on all patients, without the need to match a blood type. It's used in con-

junction with blood transfusions rather than as a substitute for them.

Over the next two years, 20 to 30 trauma patients will be included in the study of Diasprin Cross-Linked Hemoglobin, said Dr. Mary Nan Mallory, an assistant professor in the U of L medical school's emergency medicine department.

Mallory, who is head investigator for the project, said the number of potential test subjects is limited because only about three patients who have suffered severe blood loss are brought to the emergency room each month.

Half the patients in the study will

get the new product and the other half will get a saline solution. Both groups will be monitored and get regular blood tests to track their progress.

Mallory said that immediately after a serious injury causing blood loss, the body tends to direct circulation primarily to the heart, liver, lungs and other vital organs — and to limit blood flow to the extremities.

But as blood loss continues, the body "gives up," Mallory said. Blood pressure drops and circulation no longer is directed to vital organs, causing them to be damaged and many patients to die.

The new product, produced by California-based Baxter Healthcare Corp., shows promise of not only increasing blood pressure but also of restoring the flow to the vital organs, Mallory said. If that happens, damage from oxygen deficiencies may be limited, and the death rate for these patients might be reduced.

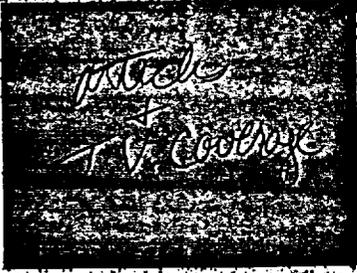
While patients' permission is usually required to include them in medical experiments, U of L researchers will be able to use the product on patients even if they are unconscious and no relatives are available to provide consent.

That is permitted under a "waiver

of informed consent" procedure recently authorized by the Food and Drug Administration. The waiver was approved for studies in which the potential benefits outweigh the possible risks. Side effects from the blood product may include nausea and pain in the back, abdomen and muscles.

Mallory said the new product is used only at the beginning of treatment in the emergency room, "so we won't be able to take it back" from patients who don't want to continue with the research.

But patients can decide later not to undergo monitoring or blood testing that will be part of the study.



Blood-loss survival product to be tested

ASSOCIATED PRESS

LOUISVILLE — University of Louisville researchers will start testing a new product that they hope will increase the survival rate of patients who have lost a lot of blood.

During the next two years, 20 to 30 trauma patients will be included in the study of Diasprin Cross-Linked Hemoglobin, said Dr. Mary Nan Mallory, an assistant professor in the U of L medical school's emergency medicine department.

Preliminary studies have shown that Diasprin Cross-Linked Hemoglobin has promise for restoring blood pressure and circulation to people who have lost about half of their blood from trauma.

Almost half of patients with severe blood loss die within 28 days of their injury, in large part because of damage to vital organs caused by lack of oxygen, which is carried by the blood.

The new product, produced by California-based Baxter Healthcare Corp., is made from outdated human blood stored in blood banks. The blood is filtered, heated and undergoes other treatment. The result is a product

that can be used on all patients, without the need to match a blood type. It's used in conjunction with blood transfusions rather than as a substitute for them.

Mallory, head investigator for the project, said the number of potential test subjects is limited because only about three patients who have suffered severe blood loss are brought to the emergency room each month.

Half the patients in the study will get the new product and the other half will get a saline solution. Both groups will be monitored and get regular blood tests to track their progress.

Mallory said that immediately after a serious injury causing blood loss, the body tends to direct circulation primarily to the heart, liver, lungs and other vital organs — and to limit blood flow to the extremities.

But as blood loss continues, the body "gives up," Mallory said. Blood pressure drops and circulation no longer is directed to vital organs, causing them to be damaged and many patients to die.

inside UofL

Feds he
in dem
Ophtha
beques

July 18, 1997

A newspaper for the faculty and staff of the University of Louisville

Synthetic blood is new trauma treatment

By Randi Hansen
Staff Writer

U of L researchers will study a synthetic blood product that may allow emergency physicians to speed treatment of patients who have suffered severe blood loss.

The product, Diasprin Cross-Linked Hemoglobin (DCLHb), is prepared from chemically modified human red blood cells. It is sterilized and pasteurized, and can be frozen for up to one year. Most importantly, DCLHb can be used on anyone, and does not require a match with the patient's own blood type.

Study criteria dictate that only the most seriously injured patients, those with severe shock and bleeding, are eligible for enrollment. These patients are at the greatest risk of death.

All patients will receive the best medical care available, stressed Mary Nan Mallory, principal investigator for the Kentucky study. The DCLHb treatment will be administered as additional therapy. The study is nationally randomized, which means of those patients at all participating centers who fit treatment parameters, approximately half will receive this additional treatment step; the other half will not.

"Diasprin holds great promise for our patients with severe traumatic injury," said Mallory, who also is a physician in U of L's emergency medicine department. Even after surviving severe blood loss, Mallory explained, a patient still risks death in the first month due to the initial damage to internal organs and tissues. "We want to find out through this study," she added, "if the use of DCLHb can decrease the number of deaths that occur in that 28-day window."

The U.S. Food and Drug Administration has authorized U of L to study the product in its trauma center during a two-year trial. U of L and federal research protocols dictate that a patient must give informed consent before being enrolled in any clinical trial. However, patients who have suffered severe trauma and loss of



Mary Nan Mallory

blood — the type of case for which U of L's DCLHb study was designed — sometimes are injured too seriously to give informed consent, nor can next of kin be located in time to administer treatment.

In such cases, U of L will use a waiver of informed consent recently authorized by the FDA for just such contingencies. The waiver allows researchers at U of L Hospital to administer DCLHb before informed consent can be given. The study was reviewed and approved by U of L's Human Studies Committee, which oversees the protection of human subjects in research. Patients and their families, however, have the right to withdraw from the trial at any time after they have been

informed.

The committee also has outlined a comprehensive "public disclosure" plan. A three-week program of advertising and publicity is under way; its aim is to inform local residents of the study and the possible use of the FDA waiver.

A special telephone number, 1-800-763-4916, has been set up to allow community members to comment and/or submit questions. Callers who have questions can leave a message, including their telephone numbers, and a study staff member will answer such questions by return phone call. A mechanism also is available to exclude from the study those who wish.

JW

GREATER LOUISVILLE CONGREGATIONS
For Jehovah's Witnesses

Hospital Liaison Committee

1508 Beech Street
New Albany, IN 47150
(812) 944-4789

F. Hewitt
Chairman
944-4789

R. D. Caster
897-7022

J. F. Gates
367-1608

R. E. Perry
447-4886

C. R. Price
776-0307

August 8, 1997

Mrs. Mary S. Bennett RN, MSN
Director of Guest Relations
University of Louisville Hospital
530 S. Jackson Street
Louisville, Kentucky 40202

Dear Mrs. Bennett:

If you should need any more of the material that you requested, please let us know as we do appreciate the interest that you have shown in our work, as well as the effort that you have put forth to improve our communication with your facility.

As we have often stated, our aim is cooperation and not confrontation; however, we feel that the experimental treatment of patients as stated in the Courier Journal of July 30, 1997 will be a problem to be addressed.

As early as 1993 our research revealed that this product prepared by Baxter Health-Care Corporation was from blood whose shelf life had expired, and is essentially "recycled" for the use stated in the article.

The "waiver of informed consent" as discussed in the article raises ethical and legal concerns as to the correctness of this action, and whether FDA has the authority to initiate such. Clearly, more vigilance on our part will be required to deal with any situation that may develop.

This seems to be an appropriate time to make a request for a list of doctors that are favorable to treating Jehovah's Witnesses in the field of Anesthesiology, Neonatology, Oncology, Radiation Oncology, Orthopedics, and any other area where blood could become an issue so that we can direct our people to these cooperative doctors, when necessary.

We are not expecting any miracles, only reasonable, alternative treatment.

Thank you for your very efficient handling of our problems in the past, and we look forward to an improved and continuing interchange along with positive solutions.

Yours Sincerely,

Louisville Hospital Liaison Committee

Department of Emergency Medicine

School of Medicine
University of Louisville
Louisville, Kentucky 40292
(502) 852-5689
FAX: (502) 852-0066

UNIVERSITY of LOUISVILLE

September 2, 1997

Louisville Hospital Liaison Committee
Greater Louisville Congregations for Jehovah's Witnesses
1508 Beech Street
New Albany, IN 47150

Dear Liaison Committee,

I received a copy of your letter addressed to Mary Bennett, Director of Guest Relations for University of Louisville Hospital, concerning **Diaspirin Cross-linked Hemoglobin**, the product produced by Baxter Healthcare Corporation. I understand why your committee would have concerns about this hemoglobin based product. You may be aware this research protocol excludes patients who have known objections to blood or blood products.

It is our institution's practice to examine personal effects of a patient that is admitted and is unable to communicate with the hospital personnel. With this in mind, it is imperative to reiterate to your congregations, in this area, to carry an identifying card in their wallet/purse. We have found, in the past, this is the most successful way to identify a person's transfusion wishes.

The University of Louisville Hospital and its personnel want to carry out each and every patient's wishes. If you have any additional questions or concerns please do not hesitate to call 1-800-763-4916.

Sincerely,



Mary Nan Mallory, M.D.
Assistant Professor
Department of Emergency Medicine

JW

GREATER LOUISVILLE CONGREGATIONS
For Jehovah's Witnesses

Hospital Liaison Committee

1508 Beech Street
New Albany, IN 47150
(812) 944-4789

F. Hewitt
Chairman
944-4789

R. D. Caster
897-7022

J. F. Gates
367-1608

R. E. Perry
447-4886

C. R. Price
776-0307

September 8, 1997

Mary Nan Mallory, M.D.
Assistant Professor
Department of Emergency Medicine
University of Louisville
Louisville, Kentucky 40292

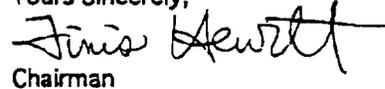
Dear Doctor Mallory:

Thank you for your prompt reply concerning Diaspirin and your comments which clears up the matter to our satisfaction. We also appreciate the reminder about our Advance Medical Directive as we still have training to complete with our folks so that they will be diligent in this matter.

Your policy of respecting a patients rights is greatly appreciated, for often a facility will be obstinate in this regard and create trauma for all concerned.

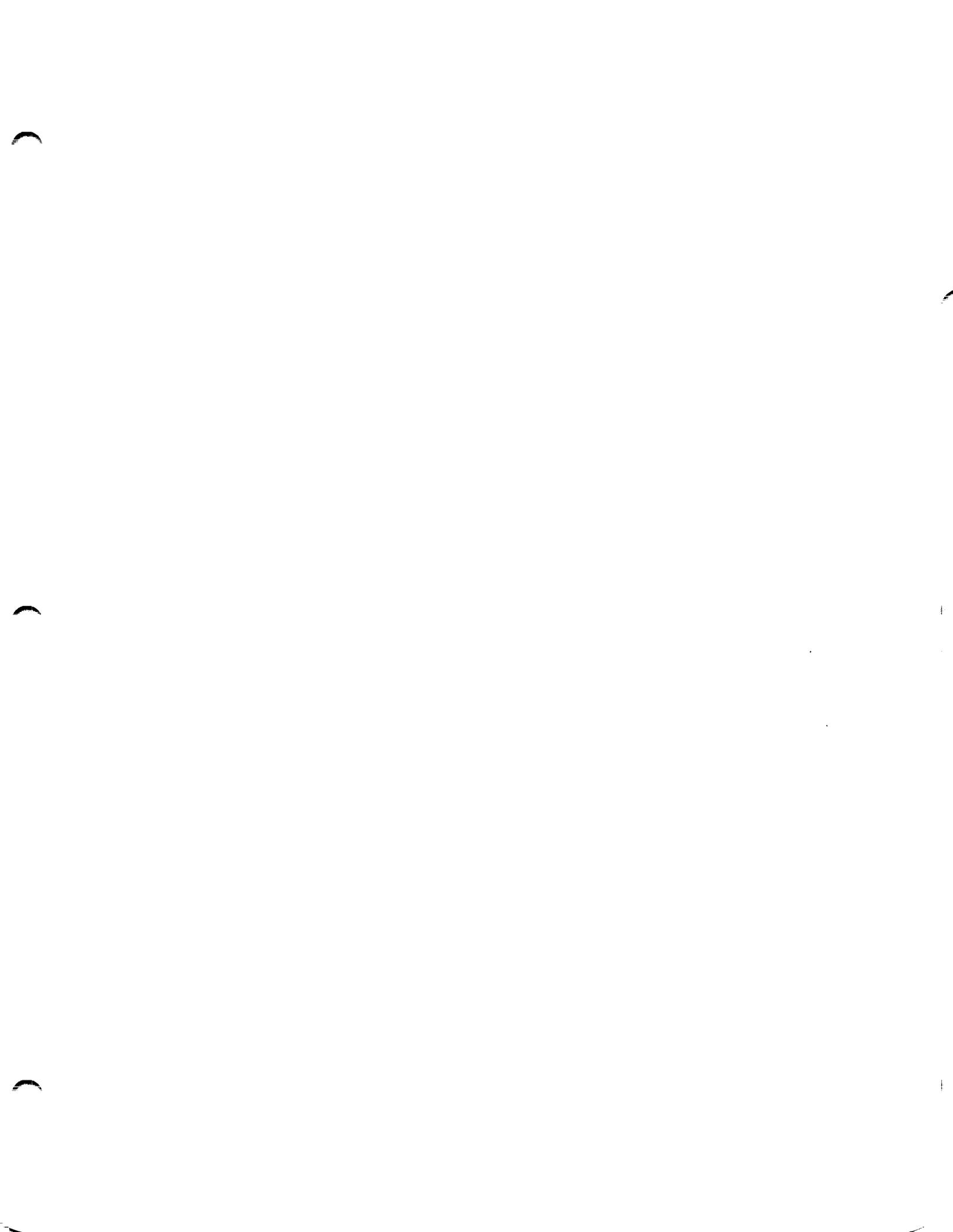
If there is any occasion where some in your group are curious about our stand and want to interact with us, we would view this as a priviledge and an opportunity to create in atmosphere of mutual understanding.

Yours Sincerely,



Chairman

Louisville Hospital Liaison Committee



MOGLOBIN

ITER=ast

PAGE#=21

NEWSCAST=11

TALENT=CHO/LLY

GRAPHIC=

(***CRAIG ***)

A NEW PRODUCT BEING TESTED IN EMERGENCY ROOMS ACROSS THE COUNTRY MAY SAVE YOUR LIFE.

(***LORI***)

IN THE NEXT FEW MONTHS, A SELECT GROUP OF TRAUMA PATIENTS IN WAVE COUNTRY WILL RECEIVE A MODIFIED HEMOGLOBIN CALLED D-C-L-H-B.

WAVE THREE NEWS REPORTER ANDREA STEPHENSON EXPLAINS.

TAKE PKG

FONT=U of L Hospital/Louisville

FONT=Dr. Mary Nan Mallory/Attending Physician

FONT=Andrea Stephenson/Reporting

OUTCUE=SOC

RUNS=

TOTAL=00:16

Wave 3

==P HEMOGLOBIN

RITER=ast

PAGE#=#

NEWSCAST=#

IN ROOM 9 AT U OF L HOSPITAL, THE EMERGENCY STAFF TREATS THE AREA'S MOST CRITICAL PATIENTS: THEY HOPE RESEARCH ON A NEW HEMOGLOBIN PRODUCT WILL INCREASE SURVIVAL RATES BY 20%.

(tape :12) ("the patients most sick, those are the ones in the study, they have lost a large percentage of their blood's volume through trauma, blunt trauma like in a car accident or punctures like gunshots and stabbings.")

RUNS=00:13

THE PRODUCT, CALLED DCLHB...HAS BEEN SHOWN TO SPEED OXYGEN TO VITAL ORGANS WHEN PATIENTS HAVE LOST A SIGNIFICANT AMOUNT OF BLOOD. THE CHEMICALLY ALTERED HUMAN HEMOGLOBIN PRODUCT IS MADE FROM EXPIRED BLOOD FROM BLOOD BANKS...A PHARMACEUTICAL COMPANY HAS FIGURED OUT A WAY TO TAKE RED BLOOD CELLS-THE OXYGEN CARRYING CELLS- AND PURIFY THEM.

(TAPE 25:14 stand up) ("The hemoglobin will be used in addition to all the other essential fluids, it does not require a cross-match and can be used on anyone.")

runs=00:10

ADDITIONALLY, DOCTORS SAY DCLHB CUTS DOWN ON TRANSFUSION RELATED INFECTIONS AND REACTIONS. ANOTHER BENEFIT EMERGENCY CARE WORKERS SAY WILL HELP THEIR PATIENTS IN THE LONG RUN.

(tape 9:18) ("We're still seeing patients die in Intensive Care in the first month from damage done to organs in the first hour before their holes are fixed. We want to reverse that trend, and we hope this is it.")

runs=00:14

ANDREA STEPHENSON, WAVE THREE NEWS.

OUTCUE=soc

RUNS=-

TOTAL=01:18

T HEMOGLOBIN

RITER=ast

PAGE# =

NEWSCAST =

TALENT=LLY

GRAPHICS =

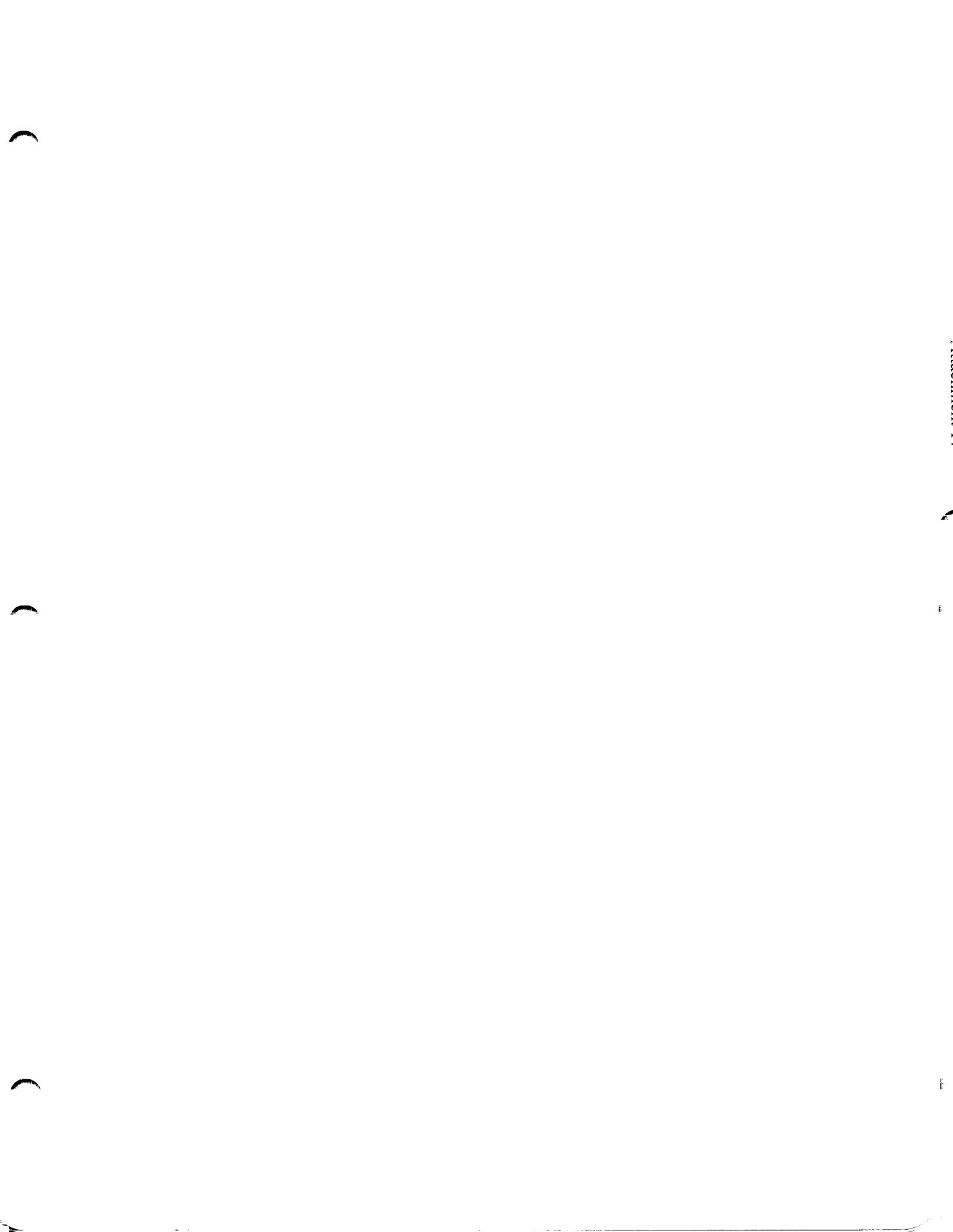
(***LORI***)

THE PRODUCT WILL BE GIVEN IN ADDITION TO BLOOD...

DOCTORS WILL PICK THE PATIENTS THEY THINK WILL BENEFIT FROM THE NEW PRODUCT.

IF FAMILY MEMBERS DON'T WANT THEIR LOVED ONES TO PARTICIPATE IN THE STUDY,
THEY CAN DECLINE TREATMENT AT ANY TIME.

TOTAL=00:13





University of Pittsburgh
Medical Center

News Bureau

CONTACT: Frank Racziewicz
EMAIL: raczkf@A1.ISD.UPMC.EDU
Susan Manko
PHONE: (412) 647-3555
FAX: (412) 624-3184

FOR IMMEDIATE RELEASE

UPMC TO STUDY BLOOD SUBSTITUTE IN TRAUMA PATIENTS

PITTSBURGH, July 1 -- Researchers at the University of Pittsburgh Medical Center (UPMC) are participating in a study to determine the effectiveness of a new blood substitute in the treatment of trauma patients with severe blood loss. It is hoped that this experimental blood substitute will help to reduce deaths from trauma. About 40 sites nationwide are participating in the study.

A patented, experimental blood substitute will be given to trauma patients to treat the harmful side effects of severe blood loss and possibly prevent death. This study is made possible by guidelines recently adopted by the Food and Drug Administration (FDA) that allow consent to be waived in studies of emergency therapies for patients in life-threatening situations. Due to the nature of this study, patient consent may not be possible.

Obtaining advance consent from family members also will be difficult because the blood substitute must be given within one hour of hospital arrival. Patients or their family members will be notified as soon as possible about the study and given the option of whether or not to continue.

-more-

2811 O'Hara Street, Pittsburgh, Pennsylvania 15213 412-624-2607 412-647-3555 Fax: 412-624-3184
Jane Duffield, Director Home phone: 412-363-7058

Page -2-

About 20 patients will be enrolled in the study at the UPMC. Half will receive the blood substitute and half will receive a saline solution. Patients also will be given all current standard treatments.

The blood substitute, developed by Baxter Healthcare Corporation, is derived from human red blood cells. A specialized filtration and heating process allows the finished product to be safe from viruses. The solution carries oxygen and therefore has significant application potential in trauma situations where large amounts of blood loss can result in a lack of oxygen to vital tissues. It is easily stored in emergency departments and can be immediately transfused in trauma patients.

For additional information about the University of Pittsburgh Medical Center, please access our website at <http://www.upmc.edu>.

#

lk\7-1-97

[▶ UPMC HOME](#)[▶ SEARCH](#)[▶ UTILITIES/HELP](#)[▶ DIRECTIONS](#)[▶ CONTACT](#)

UPMC TO STUDY BLOOD SUBSTITUTE IN TRAUMA PATIENTS

PITTSBURGH, July 1, 1997 -- Researchers at the University of Pittsburgh Medical Center (UPMC) are participating in a study to determine the effectiveness of a new blood substitute in the treatment of trauma patients with severe blood loss. It is hoped that this experimental blood substitute will help to reduce deaths from trauma. About 40 sites nationwide are participating in the study.

A patented, experimental blood substitute will be given to trauma patients to treat the harmful side effects of severe blood loss and possibly prevent death. This study is made possible by guidelines recently adopted by the Food and Drug Administration (FDA) that allow consent to be waived in studies of emergency therapies for patients in life-threatening situations. Due to the nature of this study, patient consent may not be possible.

Obtaining advance consent from family members also will be difficult because the blood substitute must be given within one hour of hospital arrival. Patients or their family members will be notified as soon as possible about the study and given the option of whether or not to continue.

About 20 patients will be enrolled in the study at the UPMC. Half will receive the blood substitute and half will receive a saline solution. Patients also will be given all current standard treatments.

The blood substitute, developed by Baxter Healthcare Corporation, is derived from human red blood cells. A specialized filtration and heating process allows the finished product to be safe from viruses. The solution carries oxygen and therefore has significant application potential in trauma situations where large amounts of blood loss can result in a lack of oxygen to vital tissues. It is easily stored in emergency departments and can be immediately transfused in trauma patients.

###

MEDIA CONTACT: Frank Raczkiwicz

TELE: (412) 647-3555

FAX: (412) 624-3184

EMAIL: RACZKI@ALISD.UPMC.EDU

[Top of Page](#) | [News Bureau Home Page](#)

[News Releases](#) | [Archives](#) | [Biographies](#) | [Contact The News Bureau](#)

[UPMC Home](#) | [Search](#) | [Utilities/Help](#) | [Directions](#) | [Contact the UPMC](#)

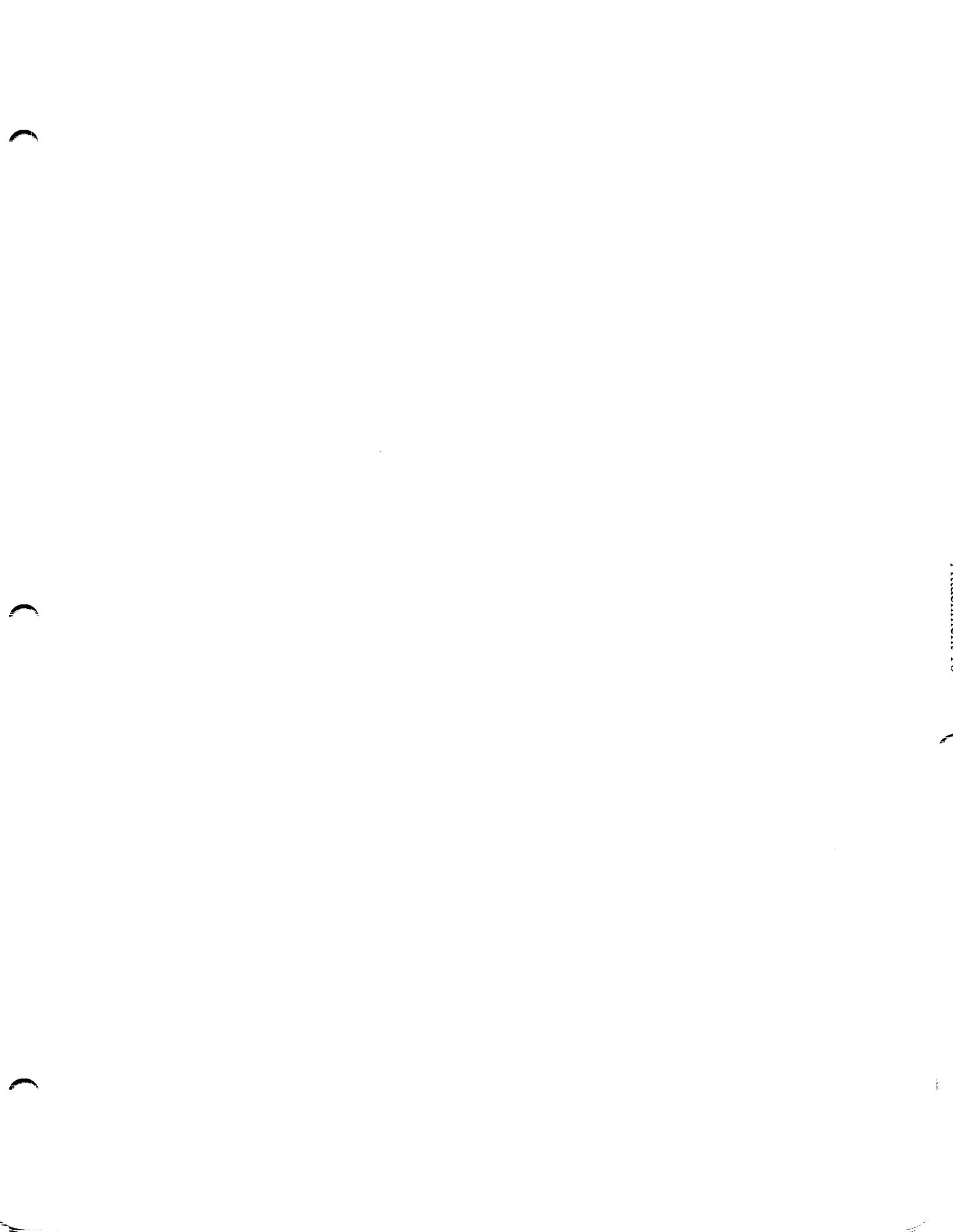
© 1997 University of Pittsburgh Medical Center



UNIVERSITY *of* PITTSBURGH MEDICAL CENTER

UPMC News Bureau

- [NEWS RELEASES](#)
- [ARCHIVES](#)
- [BIOGRAPHIES](#)
- [CONTACT US](#)



Univ Of Pittsburgh To Study Baxter's Blood Substitute >BAX

112 Words

1227 Characters

07/02/97

12:16

Dow Jones News Service

(Copyright (c) 1997, Dow Jones & Company, Inc.)

PITTSBURGH (Dow Jones)--The University of Pittsburgh Medical Center said it will participate in a study to determine the effectiveness of

- * Baxter International Inc.'s (BAX) blood substitute in treating trauma patients with severe blood loss.

In a press release Wednesday, University of Pittsburgh Medical Center said about 40 sites are participating in the study.

- * Baxter Healthcare Corp.'s patented, experimental blood substitute, derived from human blood cells, will be given to trauma patients to treat the side effects of severe blood loss and possibly prevent death. Due to the nature of the study, patient consent may not be possible.

Baxter is a medical products and services company.

(END) DOW JONES NEWS 07-02-97

*** UPMC to Study Blood Substitute in Trauma Patients****304 Words****2317 Characters****07/02/97****11:18****PR Newswire****(Copyright (c) 1997, PR Newswire)**

- PITTSBURGH, July 2 /PRNewswire/ -- Researchers at the University of Pittsburgh Medical Center (UPMC) are participating in a study to determine the
- * effectiveness of a new blood substitute in the treatment of trauma patients
 - * with severe blood loss. It is hoped that this experimental blood substitute will help to reduce deaths from trauma. About 40 sites nationwide are participating in the study.
 - * A patented, experimental blood substitute will be given to trauma patients to treat the harmful side effects of severe blood loss and possibly prevent death. This study is made possible by guidelines recently adopted by the Food and Drug Administration (FDA) that allow consent to be waived in studies of emergency therapies for patients in life-threatening situations. Due to the nature of this study, patient consent may not be possible.

- Obtaining advance consent from family members also will be difficult because
- * the blood substitute must be given within one hour of hospital arrival.

Patients or their family members will be notified as soon as possible about the study and given the option of whether or not to continue.

- About 20 patients will be enrolled in the study at the UPMC. Half will
- * receive the blood substitute and half will receive a saline solution. Patients also will be given all current standard treatments.
 - * The blood substitute, developed by Baxter Healthcare Corporation, is derived from human red blood cells. A specialized filtration and heating process allows the finished product to be safe from viruses. The solution carries oxygen and therefore has significant application potential in trauma situations where large amounts of blood loss can result in a lack of oxygen to vital tissues. It is easily stored in emergency departments and can be immediately transfused in trauma patients.

For additional information about the University of Pittsburgh Medical Center, please access its website at <http://www.upmc.edu>.

/CONTACT: Frank Raczkiwicz, email, raczki@A1.ISD.UPMC.EDU, or Susan Manko, 412-647-3555, or fax, 412-624-3184, both of UPMC/

11:03 EDT

Researchers to study blood substitute in trauma patients

The University of Pittsburgh Medical Center (UPMC), Pittsburgh, Pa., is one of about 40 sites nationwide that have been asked to help determine the effectiveness of a new treatment for trauma victims with severe blood loss. The study involves a patented, experimental blood substitute that will be given to adult patients with life-threatening injuries. The blood substitute, developed by Baxter Healthcare Corp., will be given for emergency treatment along with standard therapy, including blood. The blood substitute is derived from human red blood cells and is heated and filtered to make it safe from viruses. Typical side effects seen in other studies include temporary increase in blood pressure, yellowing of the skin, and reddening of the urine.

The U.S. Food and Drug Administration (FDA) requires that new drugs and therapies be tested in human patients before approval for marketing. Patients or their family members must give their consent before taking part in a research study. Recently, the FDA ruled that under strict circumstances unconscious patients whose lives are in danger or for whom there is no one available to consent may be given experimental treatment when there is no proven alternative therapy.

In accordance with the revised FDA guidelines, UPMC researchers would like to make this experimental blood substitute available to unconscious trauma patients who do not have a family member available for consent. Patients or their families would be notified as soon as possible about their inclusion in the research study.

The FDA requires potential study sites to notify the public for comment before the study may proceed. Please address comments to:

Andrew Peitzman, MD
Department of Surgery, Room A-1010
UPMC
200 Lothrop St.
Pittsburgh, PA 15213-2582
or call (412) 648-9560

or

Dennis Swanson, MS
University of Pittsburgh
Institutional Review Board
219 Nesc-Barkan Building Annex
3811 O'Hara St.
Pittsburgh, PA 15213-3593
or call (412) 647-7644



UNIVERSITY of PITTSBURGH
MEDICAL CENTER

P7238 YJ/RD 7/97

Information Summary for the City of Pittsburgh Commission on Human Relations

Study Title: The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock

Overview

Physicians at the University of Pittsburgh Medical Center (UPMC) plan to take part in a clinical research study of a modified human hemoglobin (blood) solution made by Baxter, called "diaspirin cross-linked hemoglobin" (DCLHb). The subjects in this study will be victims of severe traumatic injury (for example, a motor vehicle accident or a gunshot wound) who are brought to the emergency room in shock with life-threatening blood loss. All subjects entered into the study will receive all available standard treatments for their injury. In addition, half of the subjects will receive DCLHb through a vein, and the other half will receive a salt-water solution. The subjects will be carefully monitored. Independent experts will monitor safety throughout the study. At the end of the study, the number of subjects in each group who survive will be compared, to determine if DCLHb saved lives.

Under a new regulation of the Department of Health and Human Services and the Food and Drug Administration, this research may be done with an exception to the usual procedure for obtaining a subject's written consent to participate. The study physicians and the University of Pittsburgh Institutional Review Board are seeking your questions and comments, on behalf of the community, about this research.

DCLHb

To survive, the body's vital organs and tissues must have a constant supply of oxygen. Oxygen is breathed into the lungs, where it is transferred to small blood vessels. Hemoglobin is the part of the blood that carries oxygen through the blood vessels to the tissues. When life-threatening blood loss occurs, the body may have too little hemoglobin to carry enough oxygen for survival. The usual treatment is to give fluids and blood that has been donated and stored. However, stored blood loses some of its ability to carry oxygen and may cause allergic reactions if it is not matched to the victim's own blood type. DCLHb is a modified hemoglobin solution made from human blood cells that have been filtered and pasteurized. These processes add extra steps to make the solution safe from viruses. DCLHb can carry more oxygen than stored blood and does not need to be matched to the patient's blood type. Just like stored blood, it must be given immediately to replace lost hemoglobin when life-threatening blood loss has occurred.

DCLHb has been studied in patients for four years. These studies have included many different types of patients, including those with trauma, shock, stroke, kidney failure, critical illness, overwhelming infection, acute anemia, and major surgery. Over 700 patients have participated, of which more than 350 have received DCLHb. These studies

have involved 26 hospitals or universities in the United States and eight other countries. Before DCLHb can be accepted as a standard treatment, however, its effectiveness must be tested even more extensively in patients.

Study Subjects

The subjects in this study will be adult victims of severe traumatic injury who are brought to the UPMC Trauma Center and have shock with life-threatening blood loss. With standard available treatments (fluid therapy, blood transfusion, surgery), about 40% of victims with this degree of injury will die. Victims of any race, ethnic group, sex, religion, or HIV status will be equally eligible for the study. Only patients who are younger than 18 years, are pregnant, object to the use of blood products (Jehovah's Witness), have severe head injuries, or whose heart has stopped will be excluded from the study.

Study Procedures

Subjects in the study will receive all standard treatments and procedures normally used to treat severe injury and shock, including fluid therapy, blood transfusion, and surgery if necessary. In addition to these standard treatments, subjects will be randomly chosen (like a coin toss) to also receive either DCLHb or a salt water solution. The solution will be given through a vein, similar to the way in which blood is given.

During the study, the physicians will collect information from the patient through physical examinations and laboratory tests, including urine samples and blood samples withdrawn from a vein or an artery. These procedures are similar to the usual tests done for a patient in this severely ill condition.

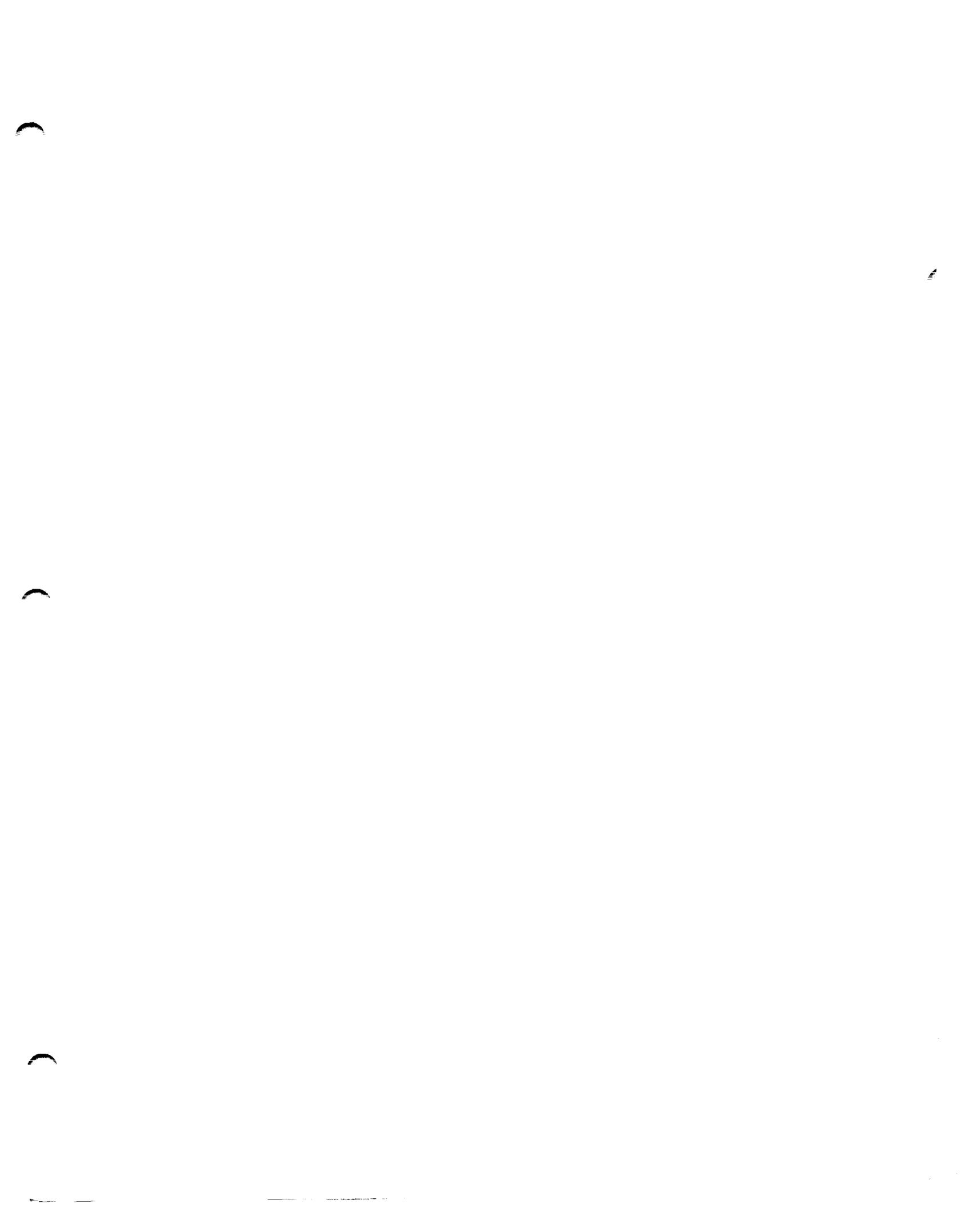
The study team will also evaluate the patient's vital signs (blood pressure, heart rate, breathing rate, breathing effort) several times during the first 48 hours of the study. On days 4, 7, 10, 14, 21, and 28 after the study starts, additional blood samples and vital sign measurements will be taken. The patient's participation in the study lasts for a total of 28 days.

Consent Procedure

Research on emergency treatments like DCLHb is difficult to do, because the treatments must be given immediately, the subject is often unable to respond, the subject's family may not be available, or the subject's identity may be unknown. In the past, such research was done without the subject's consent. In 1993, however, all emergency research without consent was stopped until a new federal regulation could be developed that would offer more protection of subjects' rights. Many experts in the fields of medicine and ethics were involved in developing this regulation. After a period of public commentary on the new regulation, it became final in November 1996. The regulation states that under certain circumstances new treatments may be tested in emergency situations before written consent is obtained. It requires that (1) each subject may benefit by participating in the

study, (2) the new treatment has the potential to save lives of future patients, (3) current treatments for these patients are not very effective, and (4) the study could not be done with the usual written consent procedure. The FDA determined that this study of DCLHb meets these criteria.

As soon as an eligible subject for the study is identified in the emergency room, every effort will be made to obtain the consent of the subject or a family member or legally authorized representative before giving DCLHb. If, however, consent cannot be obtained in the required time frame for giving DCLHb, DCLHb (or salt water) will be started before consent. As soon as possible, the subject or a family member or representative will be notified about the study. If that person does not want the subject to remain in the study, it will be stopped immediately.



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

Andrew B. Peitzman, M.D.; Principal Investigator

Marilyn J. Borst, M.D.; Co-Principal Investigator

Co-Investigators:

Anita Courcoulas, M.D.

Donald Yealy, M.D.

W. David Watkins, M.D., Ph.D.

- [This slide will be that of a Car Wreck]

Why do this study?

- 150,000 people die each year due to traumatic injuries
- Effect of severe trauma is immediate and catastrophic
- 40% of victims with severe traumatic injuries will die
- Current treatments are not very effective

Objective

- To determine if the death rate in this patient population can be reduced by 25%

Who will benefit?

- Each patient may benefit
- Potential to save the lives of trauma patients in the future

What is DCLHb?

- Modified human hemoglobin solution
- Carries oxygen
- May increase delivery of oxygen to tissues
- No need for cross-match to patient's blood type
- Can be given immediately
- Longer storage life
- Can be stored anywhere

[This slide will be that of a Bag of DCLHB
(one of Baxter's slides)]

Is it safe?

- This study has been fully reviewed and cleared by the Food & Drug Administration (FDA), including the safety information.
- DCLHb has been studied extensively in patients for 4 years.
- DCLHb safety has been favorably reviewed by over 25 Internal Review Boards (IRBs) and numerous regulatory agencies around the world.

- Independent experts will monitor patient safety during the study.
- Positive risk/benefit profile in this study.

What are the side-effects?

- Temporary changes in some lab test results (no clinical effects)
- Temporary yellowing of skin (break-down product of DCLHb)
- Temporary red color in urine (DCLHb is red)

Study "Specifics"

- Inclusion criteria
 - victims of severe traumatic injury who have life-threatening blood loss
 - victims of any race, ethnic groups, sex, religion, HIV status
 - 18 years of age or older
 - low blood pressure and rapid heart rate
 - evidence of insufficient oxygenation
- Estimated 2-4% of all trauma patients

- All patients will receive all standard therapies
 - intravenous fluids
 - blood transfusions
 - surgery, if necessary
- In addition to standard therapies
 - 1/2 of patients will receive DCLHb
 - 1/2 of patients will receive a salt-water solution
- Random equal chance (like a coin toss) to receive either DCLHb or salt-water solutions.

- Exclusion criteria
 - younger than 18 years
 - pregnant
 - object to the use of blood products
 - Jehovah's Witness
 - severe head injury
 - imminent death
 - hospitalization >60 minutes prior to infusion
 - known injury time >4 hours prior to infusion

Why do we need to do this study with
Exception from Informed Consent?

- Difficult to obtain prospective consent
 - traumatic injuries occur unexpectedly
 - victims may be unconscious
 - identity is often unknown
 - little time to contact family member / legal representative
 - treatment must be given promptly
- * FDA has given approval for this study to be done with exception from informed consent

How will we attempt to obtain informed consent?

- Identify patient by any possible means
- Attempt to contact family member / legal representative
 - social workers

If unable to obtain consent prior to infusion

- notify patient / family member / legal representative as soon as feasible
- allow them to express their wishes to either:
 - (1) continue full participation in the study
 - (2) continue participation limited to safety observations including the determination of basic health condition at 28 days
 - (3) discontinue participation

Who will be participating in this study?

- Multiple university and community medical centers
 - up to 40 centers
- 20-30 patients per center
 - 850 patients total

[This slide will be that of an Accident Scene]

-will use this slide to make concluding remarks that we hope this new tx will improve future care of trauma pts

[The following slides will be Extra Slides to have in case they are needed during the discussion session]

none were used.

PITTSBURGH COMMISSION ON HUMAN RELATIONS

MINUTES
May 5, 1997

Attendance: Harry Kusselman, Chair
Father Lou Vallone
Curtis Smith
Christine Williams
Elizabeth Pittinger
Charles House, Jr.

Famela Golden
R. J. Samson
Robert McClenahan
John E. Grice

Staff: Charles Morrison, Director
Connie Mlakis Zatek
George Monroe
Kevin Trower, Legal Counsel
Yancy Miles

Guests: Marianne Jackson, Mayor's Office
Dave Goldberg, Controller's Office
Constance Wellons, former Commissioner
Bernie Cohen-Scott, former Commissioner

I. CALL TO ORDER

The meeting was called to order at approximately 8:35 p.m. by Harry Kusselman, Chair.

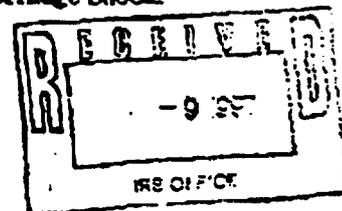
II. ADOPTION OF MINUTES

Commissioner Kusselman asked that an additional sentence be noted on page 4 regarding the discussion of the Motions Commissioner: "Commissioner Samson is removed from the Compliance Review Section during the term of her office as Motions Commissioner." He also noted that several typographical errors must to be corrected before distributing the official Minutes of the meeting.

With the above addition and corrections noted, the Minutes of the April Commission meeting were unanimously adopted upon motion of Commissioner John Grice and second by Commissioner Charles House, Jr.

III. INSTITUTIONAL REVIEW BOARD REQUEST FOR COMMENTS

Dr. Dennis Swanson of the University of Pittsburgh Institutional Review Board briefly introduced members of the Review Board and his staff: Dr. Pletsman, Dr. Marilyn Borscht, Nell Schielgel, Dr. Ted Delbridge, Jeannie Barone and Dr. Watkins. Dr. Borscht presented a summary of the "Efficacy Trial of Dapsirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhage Shock."



CHR Minutes
May 6, 1997
Page 2

Dr. Boracht stated that DCLFb is a solution of modified human hemoglobin which has been cleaned of individual properties. In laboratory tests and during the first four years of clinical study, this solution has been administered to more than 360 patients and has been effective in increasing the oxygen to tissues. Major benefits included the facts that no cross-matching is needed and the solution can be given immediately. In addition, it does not need to be refrigerated and may be stored for up to one year. Human blood must be refrigerated and has a storage life of only one month. Side effects are minimal and include temporary yellowing of the skin and/or red-colored urine.

In the proposed study at the University of Pittsburgh, DCLFb, or a placebo consisting of salt water, will be administered at random to patients over 18 years of age with life-threatening loss of blood in the immediate stages of trauma. Once it is determined that a trauma victim meets selected criteria, an envelope will be opened indicating whether or not that person is to receive DCLFb or the salt water solution. All other treatments for injuries sustained will remain standard for those injuries. Patients excluded from the study are those under 18, pregnant women and those with severe head injuries or facing imminent death.

Dr. Boracht explained that the nature of life-threatening injuries is such that prior approval and consent cannot always be obtained prior to administering the solution. Every attempt will be made to obtain consent from the patient or family as soon as possible. Once a patient, or the family, has been informed they may choose to continue with the treatment fully or in a limited capacity or discontinue it completely.

Approximately 40 other trauma centers around the country are participating in this study, therefore, a broad cross-section of the population is expected. In the Pittsburgh service area, 20-30 patients may be selected within a one-year period; only half will receive the DCLFb solution. Right now, this solution can only be administered at the trauma centers involved in the study, but later, it can be given anywhere, including on the field during war or calamity.

Commissioner Pittinger indicated that legal guardians (of mentally handicapped individuals) cannot give consent for human research; such permission or lack of objection must be sought from a family member. Dr. Swenson agreed this may prove a drawback in some instances and will check further with their attorneys.

The Institutional Review Board is comprised of members of the community with broad backgrounds in medical, legal and other fields and its their sole responsibility to determine if the proposed trial is reasonably safe, etc. The Commissioners were assured that there is no liability on the part of the Commission for serving as a sounding board for community input and comment. If the Commission decided not to participate in the review process, the Review Board would have to have consultation with the community at another level. Notice of this study will also be advertised in the local press. It is anticipated that actual start date of the study will be within next several weeks.

TOTAL P.08

PERTINENT COMMENTS: PITTSBURGH COMMISSION ON HUMAN RELATIONS

IRB #970422: Efficacy Trial of Dapsirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock, Andrew Peitzman, P.I.

May 5, 1997

1. **Re: Exclusion Criteria**
 - a. How will investigators know in advance of study enrollment if unconscious/unresponsive subjects is ≥ 18 years old, Jehovah's Witness. Recognized that this may be impossible but must d/c from study as soon as respective status is ascertained.
 - b. Re: persons declared incapacitated by the court and assigned a legally authorized representative (LAR). In the Commonwealth of Pennsylvania, LARs are not permitted to provide consent for participation in medical care/research. Recognized that it may be impossible to determine incapacitated status prior to enrollment in study, but must d/c for study as soon as respective status is ascertained.
2. **Re: Racial/Gender Considerations**
 - a. There may exist a racial/gender imbalance regarding the prevalence of severe trauma. Hence, study enrollment may not represent appropriate cross-section of population. (Peitzman comments: no racial imbalance; gender imbalance does exist. Multicenter design should adequately address concern.)
 - b. Does risk/benefit ratio of intervention differ among races/ethnic groups? (Peitzman comments: Hemoglobin is normal substrate that does not differ between races/ethnic groups therefore no difference expected. No specific data from prior human studies demonstrating a difference.)
3. Will subject assigned to receive placebo (saline) solution receive a substandard of care? (Peitzman comment: All subjects will receive standard of care with added administration of test drug or placebo.)
4. More difficult to identify/locate families of homeless, underprivileged individuals (Peitzman comment: There is an equal difficulty finding families of trauma victims.)

Newscast, July 10, 1997
Channel 4, WTAE TV
6 p.m. newscast

Introduction: A news anchor introduced the product "Well you've heard it before, a serious shortage at the blood bank, only it seems to be getting worse, that's the bad news. The good news, a new blood substitute could one day ease the strain. Medical Editor Marilyn Brooks reports."

Scene switches to people giving blood at the Downtown Central Blood Bank

Marilyn Brooks: "At first glance things seem normal. **People are giving**, but a closer look reveals it's not enough."

Janis Nickleach, Blood Bank: "We've been below normal operating level since Memorial Day Holiday and we've not been able to rebound."

Marilyn Brooks: "It takes 700 units to supply hospitals. The numbers fall far below. Blood is at a premium in Pittsburgh and the nation."

Janis Nickleach: "Older generations are becoming increasingly unable to donate and the younger generations aren't picking up the slack."

Marilyn Brooks: "That *could* eventually **hurt** patients like 42 year old Gregg Hnat, a head on collision May 28, ripped open his liver and main aorta. Surgery and 44 units of blood saved him."

Scene switches to the bedside of Gregg Hnat

Gregg Hnat, Trauma Patient: "Means a lot, very much, I can't wait to give some."

Marilyn Brooks: "It literally saved your life."

Gregg Hnat: "It really *did*. I'm very lucky to be here."

Marilyn Brooks: "He wouldn't be here without blood and that makes the constant shortage a major concern. But help may be just around the corner within the next month or two. Doctors and Trauma Units across the nation are going to be testing a new blood substitute on trauma patients with severe blood loss. It's called Diaspirin Crosslinked Hemoglobin and it has one job, that is, to save the lives of people who could otherwise die from massive blood loss."

Scene switches to a microscopic photo of blood

Marilyn continues: "Diaspirin is actually purified hemoglobin, the protein in red blood cells that carry oxygen. Its less volume and research shows that it might actually be better for trauma patients rather than the large volumes of whole blood they traditionally received."

Scene switches to interview

Dr. Fred Hachelroad, Jr., Allegheny General Hospital: "This product allows us to give a small volume of a 'medication' really, that carries oxygen equivalent to a large volume of blood."

Dr. Donald Yealy, University of Pittsburgh Medical Center: "I don't think it will be a monumental change in trauma care, but I think it'll be the first step in helping to correct a problem that right now we only have one intervention, and that's the precious product of blood."

Scene switches to a newsroom

Marilyn Brooks: "Nearly 150,000 people die every year from trauma injuries -- how many more suffer from prolonged illness. This advancement could make a difference under the new FDA consent requirements, however, Doctors can only use the blood substitute with community consent and they're working on that. Meanwhile, the blood bank needs what we all can give and a lot of patients will be very, very, grateful if we can give it."



Section of Trauma/Critical Care Surgery

J. Stanley Smith, Jr., M.D., F.A.C.S., F.C.C.M.
Robert N. Cooney, M.D., F.A.C.S.
Peter Mucha, Jr., M.D., F.A.C.S.
Sandralee Blosser, M.D., F.C.C.P.

Department of Surgery

The Milton S. Hershey Medical Center
The Pennsylvania State University
P.O. Box 850
Hershey, Pennsylvania 17033-0850
Telephone: (717) 531-4404
(717) 531-6241
Telefax: (717) 531-3649

July 11, 1997

Ms. Jean E. Vary
HSPO, Institutional Review Board
Room 6509
The Milton S. Hershey Medical Center
Hershey, PA 17033

RE: The Hemassist protocol Community Consultation

Dear Jean,

The first community consultation regarding the exception to inform consent for the hemassist protocol was held on July 5, 1997. The participants in this community consultation included Mr. & Mrs. David Richardson of Susquehanna Township, Harrisburg, Mr. & Mrs. Stewart Rutherford of Susquehanna Township, Harrisburg, Mr. & Mrs. David Werner of Eagles Mere, PA, Mrs. Diane Spahr of Danville, PA, Mr. & Mrs. Daniel Hrabko of Eagles Mere, PA and Mr. Thomas Shannon, PhD., Professors of Ethics of Worcester Polytechnic Institute, Worcester, MA.

The protocol was presented to the group who represent communities including rural Pennsylvania, middle class central Pennsylvania, and bio-ethics. The product was discussed, the principals of the protocol were discussed with the group and the exception to informed consent was discussed at length as it would relate to the members of the group as well as their families and or their children if applicable.

The members of the group were unanimous in support of the protocol and for a product that would be of minimal risk and potentially life saving would support the exception to informed consent.

No major objections to the protocol or to the informed consent were placed.

In further related matters regarding the public information aspects of this protocol, letters to the Editor of the Harrisburg Patriot news and the Lebanon newspaper have been sent. An article has appeared in the Lancaster Intelligencer Journal. The protocol has been reviewed on WITF radio news. It has also appeared on a program called "Heart of the Matter" airing nationally. It has also appeared on AMA radio news as of July 8, 1997. The protocol has also been presented

Page 2

Ms. Jean E. Vary

RE: **The Hemassist protocol Community Consultation**

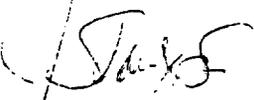
twice on WGAL-TV 8 news from Lancaster, not on the basis of our Center but from the Lehigh Valley Hospital which is also a participating Center in the multi-institutional trial.

The Community Consultation groups and public information appears to be progressing satisfactorily.

We still need to develop Community groups including the African-American and Hispanic populations of our area.

Please file this report with the protocol as a measure of our compliance with the Community Consultation and Public Information Program.

Sincerely,



J Stanley Smith, Jr., MD, FACS, FCCM
Professor of Surgery
Chief, Section of Trauma/Critical Care Surgery

JSS/kmk

jeanvary_hemassist

cc: Office file on **Hemassist Protocol**
ClinTrials and/or Baxter Health Care
Maggie Shumate
Marsha Langan

1

2

3



College of Medicine
 University Hospital · Children's Hospital
 The Milton S. Hershey Medical Center

Section of Trauma/Critical Care Surgery

J Stanley Smith, Jr., M.D., F.A.C.S., F.C.C.M.
 Robert N. Cooney, M.D., F.A.C.S.
 Peter Mucha, Jr., M.D., F.A.C.S.
 Sandralee Blosser, M.D., F.C.C.P.

Department of Surgery

The Milton S. Hershey Medical Center
 The Pennsylvania State University
 P.O. Box 850
 Hershey, Pennsylvania 17033-0850
 Telephone: (717) 531-4404
 (717) 531-6241
 Telefax: (717) 531-3649

July 17, 1997

Rev. A. Ronald Stiscia
 1852 Market Street
 Harrisburg, PA

Dear Rev. Stiscia: *Ken*

Thank you for agreeing to participate as part of our community consultation program for the upcoming HemAssist clinical trial.

Enclosed you will find several documents related to this trial including a transcript of a radio broadcast that I did for a national radio network show, "The Heart of the Matter". This should help to explain what this product is and what we are attempting to learn from this study. Also enclosed is a copy of our consent form for those people who will be able to give us consent directly for the study, as well as consent forms for family and the notification of the patient that they participated in such a study.

Please understand that this is a new form of therapy and that the blood substitute will be used for only the most severely injured patients whose life is threatened and who have a poor chance of survival. This drug will be given in addition to all of the best current standard therapy that we can offer a patient that is this severely injured.

We are very concerned about the welfare of these patients and do not wish to usurp the rights of patients to determine their treatment. However, we also recognize that it is often not possible to obtain consent in life threatening situations and many times these people come to us without information so that we can contact their families in a rapid manner.

If this product is to be of use for the future, this is the group of patients who are going to have the best chance to benefit from it. Unfortunately, this is also the group of patients who currently have a 40 percent chance of dying from their initial injuries. If we are to improve the care of these patients and increase the survival rate, we must be able to test new products on those populations that will be most in need of these new products. Our goal is to protect human rights and at the same time be able to facilitate study into these acute, life threatening conditions.

Page 2

Rev. A. Ronald Stiscia

July 17, 1997

So far this product has been tested in both animal studies and human studies using both normal human volunteers as well as bleeding patients. The product thus far appears to be safe and non-toxic and now needs to be evaluated for its effectiveness.

I would ask that you would read these pages involving the protocol summary and the transcript of the radio program and the consent forms and, if you have questions or comments regarding any of these forms please note them on the particular form and return them to me.

I would also be happy to answer any questions regarding the study or these forms. I can be reached at 531-4404 during normal daytime hours. Please do not hesitate to call if you have questions.

I am extremely appreciative of your time and help in this matter.

Sincerely,



J Stanley Smith, Jr., MD, FACS, FCCM
Professor of Surgery
Chief, Section of Trauma/Critical Care Surgery
The Milton S. Hershey Medical Center
Penn State/Geisinger Health System

JSS/kmk

ARonaldStisciaHemAssist71797

PENNSYLVANIA STATE



College of Medicine
University Hospital · Children's Hospital
The Milton S. Hershey Medical Center

Section of Trauma/Critical Care Surgery
J Stanley Smith, Jr., M.D., F.A.C.S., F.C.C.M.
Robert N. Cooney, M.D., F.A.C.S.
Peter Mucha, Jr., M.D., F.A.C.S.
Sandralee Blosser, M.D., F.C.C.P.

Department of Surgery
The Milton S. Hershey Medical Center
The Pennsylvania State University
P.O. Box 850
Hershey, Pennsylvania 17033-0850
Telephone: (717) 531-4404
(717) 531-6241
Telefax: (717) 531-3649

July 17, 1997

Mr. Sam Sherron
4119 Fawn Drive
Harrisburg, PA 17112

Dear Mr. Sherron:

Thank you for agreeing to participate as part of our community consultation program for the upcoming HemAssist clinical trial.

Enclosed you will find several documents related to this trial including a transcript of a radio broadcast that I did for a national radio network show, "*The Heart of the Matter*". This should help to explain what this product is and what we are attempting to learn from this study. Also enclosed is a copy of our consent form for those people who will be able to give us consent directly for the study, as well as consent forms for family and the notification of the patient that they participated in such a study.

Please understand that this is a new form of therapy and that the blood substitute will be used for only the most severely injured patients whose life is threatened and who have a poor chance of survival. This drug will be given in addition to all of the best current standard therapy that we can offer a patient that is this severely injured.

We are very concerned about the welfare of these patients and do not wish to usurp the rights of patients to determine their treatment. However, we also recognize that it is often not possible to obtain consent in life threatening situations and many times these people come to us without information so that we can contact their families in a rapid manner.

If this product is to be of use for the future, this is the group of patients who are going to have the best chance to benefit from it. Unfortunately, this is also the group of patients who currently have a 40 percent chance of dying from their initial injuries. If we are to improve the care of these patients and increase the survival rate, we must be able to test new products on those populations that will be most in need of these new products. Our goal is to protect human rights and at the same time be able to facilitate study into these acute, life threatening conditions.

Page 2
Sam Sherron
July 17, 1997

So far this product has been tested in both animal studies and human studies using both normal human volunteers as well as bleeding patients. The product thus far appears to be safe and non-toxic and now needs to be evaluated for its effectiveness.

I would ask that you would read these pages involving the protocol summary and the transcript of the radio program and the consent forms and, if you have questions or comments regarding any of these forms please note them on the particular form and return them to me.

I would also be happy to answer any questions regarding **the** study or these forms. I can be reached at 531-4404 during normal daytime hours. Please **do not** hesitate to call if you have questions.

I am **extremely** ~~appreciative~~ of your time and help in this matter.

Sincerely,

J Stanley Smith, Jr., MD, FACS, FCCM
Professor of Surgery
Chief, Section of Trauma/Critical Care Surgery
The Milton S. Hershey Medical Center
Penn State/Geisinger Health System

JSS/kmk
samsherronHemAssist71797

CLINICAL INVESTIGATION COMMITTEE [IRB] - PENN STATE COLLEGE OF MEDICINE

Human Investigation Abstract Form (must be typed)**Abbreviated Title** (max. 2 lines of 80 characters each)

Hemassist as an adjunct in the treatment of severe hemorrhagic shock

Principal Investigator: J Stanley Smith MD

Dep't./Div: Trauma Surgery

Study abstract. Summarize the study succinctly, using these headings: (1) Rationale, (2) Key Objectives, (3) Study Population [including controls], (4) Major Inclusion and Exclusion Criteria, (5) Allocation to Groups (if any), (6) Procedures, (7) Major Risks & Discomforts, and (8) Confidentiality. Underline several keywords. Use only one page.

Rationale: Despite optimal current trauma care, death rates remain high (40%) from severe hemorrhagic shock (Class 3 or 4) where 30-50% of the blood volume is lost. Diaspirin Cross-linked Hemoglobin solution (DCLHb or Hemassist) is a novel pasteurized human hemoglobin in buffered electrolyte solution with properties to restore blood volume, increase perfusion, carry oxygen, and increase blood pressure when given intravenously following hemorrhage.

Objective: Use DCLHb solution as a supplement to the best current standard resuscitation therapy to determine efficacy in reducing mortality and morbidity from severe traumatic hemorrhagic shock. Since the DCLHb is suspended in a balanced electrolyte solution, an equivalent volume of normal saline will be used as a volume and procedural control. Since the test article is colored red, the treating team will not be blinded, but the analysis team will be blinded. All current standard trauma therapy will be provided to the patient including fluids, blood and surgery regardless of treatment group. Besides the IV infusion of DCLHb, the only additional patient procedures for the research are blood draws.

Study Population: This is a multicenter trial attempting to enroll 850 patients from 40 trauma centers. Our goal would be 24 patients locally over a 12 month period. The randomization is 1:1 DCLHb vs. Saline. Randomization is by envelope draw at time of enrollment.

Inclusion criteria: Patients 18 years old or greater with signs of severe hemorrhage plus one of the following appearing within 60 minutes of trauma center arrival:

1. BP < 90 with heart rate > 120
2. BP < 90 with HR < 60 in premonitory rhythm
3. Base deficit > 15.

Exclusion Criteria: Minors, pregnant women, isolated head trauma, severe head injury with evidence of mass effect or herniation, shock due to spinal cord injury, pulseless arrest while in hospital, imminent death precluding resuscitative efforts, known objection to use of blood or blood products, hospitalization of > 60 minutes before infusion or more than 4 hours since accident.

Procedures: Once inclusion criteria are met, the randomization envelope is opened to reveal DCLHb or saline and infusion of 500 cc. test solution via a dedicated IV line must be accomplished within 30 minutes. If the patient is still in shock at the end of infusion, another 250 cc. is infused. If the patient remains in shock, this may be repeated once more for a maximum of 1000cc. test solution dose. Meanwhile and subsequently, all standard trauma care is provided including fluids, drugs, blood, and surgery.

Efficacy endpoints: Between group analysis of 28 day all cause mortality, organ dysfunction, blood utilization, hospital lengths of stay, ventilator days and cost.

Consent: This study meets the FDA requirements for Waiver or Exception to informed consent.

Confidentiality: The usual confidentiality applicable to medical records applies. (see attached)

Protocol
Date :

CONSENT FOR CLINICAL RESEARCH STUDY

The Milton S. Hershey Medical Center
The Pennsylvania State University
College of Medicine

Title of Project: The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock (THS 95.1)

Principal Investigator: J Stanley Smith, M.D.

Other Investigators: Robert Cooney, M.D., Peter Mucha, M.D., Kym Salness, M.D., Gordon Kauffman, M.D., Robert Conter, M.D., Walter Koltun, M.D., Jerry Glenn, M.D., Margaret Shand, R.N., Marcia Langan, R.N., Jann Mulac, R.N., Silvia Gosik, LPN, Grant Bochicchio, M.D., Marcelo DaSilva, M.D., Sandralee Blosser, M.D., Sara Service, RN.

This patient information and consent form is for use in a research study that involves patients in need of emergency therapy who do or do not have, because of their medical condition, the legal ability or capability to consent to their participation. When the patient cannot legally consent to participate, their representative should read the form knowing the pronouns "I" and "me" refer to the patient for whom they are signing.

This is to certify that I, _____, have been given the following information with respect to my participation (or the participation of _____ [patient's name], whose relationship to me is _____) as a volunteer in a program of investigation under the supervision of Dr. J Stanley Smith. Throughout the remainder of this consent form, the terms "I", "me", or "my" will refer only to the patient).

1. Purpose of the Study: I am being asked to take part in this research study because I have a life-threatening injury causing severe blood loss and shock that requires immediate therapy. Different intravenous solutions (liquids) are available to treat blood loss and shock. This research study involves an investigational solution, called diaspirin cross-linked hemoglobin (DCLHB, "HemAssist") used to treat patients suffering from severe traumatic blood loss shock. This solution is not yet approved by the U.S. Food and Drug Administration (FDA) and will not be approved until certain tests show the solution is safe (will not harm me) and effective (has good results). This study will answer these questions. Approximately 850 patients will take part in this study at 40 hospitals. Approximately 20 patients will take part at this hospital.

The purpose of this research is to determine how well this new hemoglobin solution treats or prevents the harmful effects of blood loss due to severe injury which include shock, severe illness, organ failure, or death. The standard (usual) treatment for severe traumatic shock due to blood loss includes giving intravenous fluids, including blood, rapidly through a vein plus medications and surgery, as needed. The research will give as an addition to the usual treatment 500 mls (1 pint) to

Protocol
Date :

Blood (1 teaspoonful to a tablespoonful) will be collected for laboratory tests as previously indicated before receiving any study solution and at the end of the infusion. One tablespoonful of blood will also be collected for laboratory tests at the following times: 2, 6, 12, 24, 48 hours; and 4, 7, 10, 14, 21, 28 days after the infusion.

If I am a woman of child-bearing potential, I agree to have a pregnancy test done before study drug administration to establish that I am not pregnant.

3. Discomforts and Risks: As with any treatment, it is possible that HemAssist could cause reactions or discomforts. These were seen in previously completed animal and/or human studies, or seen in studies using other hemoglobin solutions (solutions similar to HemAssist). Possible reactions that may occur from infusion with HemAssist are:

- stomach pain or cramps (gas or a bloated feeling) or constipation
- nausea or vomiting shortly after infusions (temporary)
- allergic reactions such as chills, elevated temperature, or skin rash
- general weakness or discomfort, headache, back pain, or muscle aches (temporary)
- temporary rise of blood pressure that may require treatment
- temporary jaundice (yellow skin) caused by breakdown of the hemoglobin
- a red discoloration in urine caused by passage of the hemoglobin
- abnormal kidney function
- 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
- temporary inability to do certain laboratory tests accurately due to interference by the hemoglobin
- a temporary increase in the time it takes for blood to clot
- small areas of damage in heart muscle, liver, or kidneys) (only seen in some laboratory animals thus far; blood testing in humans has not previously shown this type of damage)

Because HemAssist is an investigational solution and the effects in pregnancy have not been determined, risks to my unborn baby are unknown at this time. If I am a woman of child bearing potential, I will be tested for pregnancy and must be found negative to be included in the study.

The risks associated with drawing blood from my arm 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. This greatly reduces the painful part of repeated blood drawing. Insertion of a catheter (tube) into a blood vein or artery is part of the usual care of a critically injured patient.

Besides the risks and side effects described, additional risks are not currently known. If additional side effects are discovered, the sponsor (Baxter Healthcare) will notify my doctor. All new findings developed during the study will be provided to me as they become available.

Protocol

Date :

I understand that in the event of physical injury resulting from research neither financial compensation nor free medical treatment is provided for such physical injury by the University.

10. Voluntary Participation: My participation in this study is voluntary. I further understand that I may withdraw from this study at any time. My withdrawal from this study or my refusal to participate will in no way affect my care or access to medical services.

My participation could be terminated by my doctor or by the sponsor, Baxter Healthcare, without my consent if they feel it is in my best interest to do so. This may happen if I experience a bad side effect.

For my own safety, if I decide not to continue in this study for any reason, I should contact my study doctor to let him/her know. My study doctor may ask me to return to the clinic for a follow-up evaluation and to ask questions about any reactions I may have had since receiving the study drug.

During the study I will be made aware of any significant new findings pertaining to the use of study medication that may effect my decision to remain in this study.

This is to certify that I, or the person signing below, consents to and gives permission for my participation in this program of investigation. I understand that I will receive a signed copy of this consent form. The undersigned have read this form, and understand the content of this consent form.

Volunteer's Signature

Date

or Volunteer's Representative

Date

I, the undersigned, have defined and explained the studies involved to the above volunteer.

Investigator's Signature

Date

Consent to Continue

DRAFT

I _____ am the patient, family member or legally authorized representative of _____. I am aware that I, my family member, or person who I represent has been enrolled in the DCLHb trauma clinical trial. I have received the formal informed consent and have had a chance to consider the fact that participation in the clinical trial has already taken place, and that further participation is completely voluntary. I understand that if I/we decline to participate further, that it will not in any way influence the further care that is required in order to recover from the illness sustained as a result of the initial injuries or the subsequent care.

I do not consent to continue participation in this clinical trial.

Clinical Investigator

Print Name

Date

Signature

Date

Patient Family Member Legally Authorized Representative (Circle appropriate)

Print Name

Date

Signature

Date

If family member, indicate relationship

I am sorry that this process is abbreviated, but it is necessary to rapidly determine your preferences for your family member or person you represent, so that I may return to care for the patient. Once the situation has been stabilized, we can further discuss this protocol and review the full informed consent, that I am now providing to you.

Pick One (Family Member/Legal Representative)

I consent to the patient's participation in this clinical trial. I do not object to the use of DCLHb.

I do not consent the patient's participation in this clinical trial.

Investigator

Print Date

Signature Date

Family Member/Legal Representative

Print/Relationship Date

Signature Date

Interpreter

Print Date

Signature Date

APPENDIX H COMPLIANCE STATEMENT

21 CFR 50.24

This protocol is in compliance with the regulations as follows:

50.24 (a) (1) Catastrophic, irreversible hemorrhagic shock is a life-threatening situation with a 40% or greater mortality rate. The current optimal treatment must be improved through the use of new drugs such as DCLHb, once proven to be effective in controlled clinical trials.

50.24 (a) (2) (i) Subjects eligible for this protocol are suffering from a catastrophic traumatic event and are not able to give consent due to their medical condition.

(a) (2) (ii) DCLHb must be given as soon as possible if it is to improve survival, therefore it is not feasible to obtain informed consent, prior to administration as is similar when giving O negative blood in this situation.

(a) (2) (iii) Because of the unpredictable onset and emergent nature of their traumatic injury, there is no way to prospectively identify and consent these patients.

50.24 (a) (3) (i) This resuscitation research is in the best interest of trauma patients, since their traumatic injuries require immediate intervention which may be enhanced by using DCLHb.

(a) (3) (ii) DCLHb has been shown to increase survival in lethal hemorrhage models in both small and large animal preclinical studies. The same preclinical data have also shown that DCLHb therapy has the greatest chance of improving survival and reducing morbidity when it is provided immediately after the onset of catastrophic, irreversible hemorrhagic shock. (10,14,15) A number of additional preclinical studies have demonstrated that DCLHb administration after hemorrhage results in reduced morbidity and/or marked improvements in physiological indices. (5-9,16-22)

(a) (3) (iii) The predicted mortality is 40% in this patient population and the use of DCLHb may decrease this percentage. DCLHb is known to carry oxygen and studies to date have shown it to be non-toxic in hemorrhagic shock patients.

(a) (7) (v) If prospective consent is not feasible, a patient's family member will be afforded the opportunity to object to participation in the study if feasible during the therapeutic window. The investigator will summarize the efforts made to contact family members and provide this information as requested by the local IRB.

50.24 (b) The subjects, their legally authorized representative, or family member will be informed of the DCLHb protocol as soon as feasible, and will be afforded the opportunity to decline further participation as desired. If the legally authorized representative or family member is informed and the subject's condition improves, the subject will also be informed as soon as feasible. If a subject expires prior to notification, information about the study will be presented to the legally authorized representative or family member, if feasible.

50.24 (c) The local IRB will retain the documentation regarding the study for at least three years after completion of the study.

50.24 (d) This study will be conducted only after a new IND application has been submitted to FDA, and authorized in writing, by FDA. — Done

50.24 (e) The local IRB will notify, in writing, the sponsor and the clinical investigator if it determines that it cannot approve the study because the criteria for exception from informed consent for emergency research are not met or because of other relevant ethical concerns. The sponsor will promptly disclose this information to the FDA and the other clinical investigators who are participating or are asked to participate in this or a substantially equivalent study by the sponsor, and to the IRBs that have been, or are, asked to review this or a substantially equivalent study by the sponsor.

"THE HEART OF THE MATTER"
a special program of the National Emergency Medicine Association (NEMA)

Week: 580.7

Guest: J. Stanley Smith, Chief of Trauma Svcs, Penn State Hershey Trauma Ctr.

Topic: New blood supplement will save lives

Host/ Producer: Steve Girard

NEMA: Most people aren't familiar with the concept of blood supplements, but they are very important to those of us who are injured in auto accidents or victims of violent crime. A new product is being tested around the country which seems to be far beyond blood supplements we've had...and here to talk with us about it today is the Chief of Trauma Services at Penn State's Hershey Medical Center, Dr. J. Stanley Smith...

SMITH: There's been an attempt over the past twenty years ever since Vietnam war to try to replace in some way the use of whole blood or at least blood that has to be donated by people, so that in the military setting that there is an ability to be able to store things and not have to worry about the dating and the storage and some of the other problems you have just with the stored blood itself. So there's been an ongoing research effort ever since that time to develop essentially an artificial blood. Well, there hasn't been any real artificial blood that has come along. There are a number of different solutions that have come out of this research effort and they go into two main categories. The first is a, hemoglobin type solution and the second is a perflouorocarbon. The object of both of these solutions is they're looking for a chemical that will carry oxygen like blood does. And the perflouorocarbons and so on have not really worked to replace the blood. The hemoglobin solutions have been a little bit better, but even they cannot replace blood completely...so it still remains as a blood supplement, not a blood replacement or blood substitute.

NEMA: People in a trauma situation are in a bad way...tell me how such a blood supplement helps them, and doctors...

SMITH: Yea these people are in dire straits, they're bleeding, they're in shock, their blood pressure is low, their heart rates are fast and they have about a 40 % chance of dying. Just from the types of injuries we're looking at for this type study we need to be able to give them something to replace their blood volume and to be able to restore their blood pressure and this offers us an opportunity to do that. Currently what we're using is a saltwater type solution. Unfortunately we have to give back three times as much of the saltwater as the blood the person has lost. So this amounts to a tremendous amount of fluid. We're looking for a solution that can have the same properties as restoring the blood pressure and restoring the blood volume without having to give so much fluid back. Obviously the only thing to really replace blood is blood, and we try not to over-utilize blood and on the other hand we try not to under-utilize blood because its a fairly scarce resource right now. So that we're looking for something that can help us preserve blood supplies in these situations where people need many units of blood replaced, and at the same time be able to give enough blood that we can get these people to survive.

NEMA: You mentioned using a saline solution. What happens to it once it gets in the blood? People may not understand the process. What happens to the saline? Where does it go? And you mentioned about producing a lot of fluid...I mean where does that go in the body and how is that handled?

"THE HEART OF THE MATTER"
a special program of the National Emergency Medicine Association (NEMA)

Return to Topic List

Week: 580.5

Guest: Dr. J. Stanley Smith, Chief of Trauma Svcs./Penn St. Hershey Med. Ctr.

Topic: Blood supplement test

Host/Producer: Steve Girard

NEMA: Nearly as good as real blood...coming up...

SPOT: NEMA...the National Emergency Medicine Association...fights our worst health enemies - heart disease, stroke, trauma. Call 800-332-6362.

NEMA: In cases of severe trauma, blood supplements are used in place of whole blood...to maintain blood volume and pressure. A new supplement called hemassist is being tested at 40 trauma centers...and it carries some marked differences from its predecessors...like saline...

SMITH: This solution also would stay in the blood stream the same as regular blood. It doesn't leak like the saltwater solution and therefore we don't have to give as much of it...

NEMA: And Dr. J. Stanley Smith, trauma chief of Penn State Hershey Medical Center says hemassist is a big improvement in a big way...

SMITH: This has a property, number one, of carrying oxygen which is important...to get oxygen to the peripheral tissues of the cells...and it also seems to work on its own to help increase blood pressure more so than just giving the volume back.

NEMA: And helping a patient's oxygen and blood pressure levels during the first hour of emergency treatment goes a long way toward saving his life. The study will follow those patients for a year after their treatment. I'm Steve Girard

Send mail to info@nemahealth.org with questions or comments about this web site.

Copyright © 1997 National Emergency Medicine Assoc., Inc.

Last modified: May 15, 1997

"THE HEART OF THE MATTER"
a special program of the National Emergency Medicine Association (NEMA)

Return to Topic List

Week: 580.4

Guest: Dr. J. Stanley Smith, Chief of Trauma Svcs. Hershey Med. Ctr. PA

Topic: The search for substitute blood

Host/Producer: Steve Girard

NEMA: The search for substitute blood...coming up...

SPOT: For 15 years, the National Emergency Medicine Association has worked against stroke, heart disease and trauma. Join the effort, call 800-332-6362.

NEMA: Researchers have been trying to come up with a liquid that has the properties of blood...for use in military settings and in our trauma centers. Dr. J. Stanley Smith is trauma chief for the Penn State Hershey Medical Center...

SMITH: There's been an attempt, ever since the Vietnam war, to try to replace in some way the use of whole blood, so that in the military setting there is an ability to be able to store things, and not have to worry about the dating and the storage and some of the other problems you have just with the stored blood itself.

NEMA: Dr. Smith says the solutions that have been created are in two categories...hemoglobin and perflourocarbons...

SMITH: They're looking for a chemical that will carry oxygen like blood does. And the perflourocarbons and so on have not really worked to replace the blood. The hemoglobin solutions have been a little bit better, but even they cannot replace blood completely.

NEMA: But there is a new product being tested by Dr. Smith at Hershey and at 39 other trauma centers around the country, which is closer to the bill than ever before. More on Hemassist and its effects next time. I'm Steve Girard at The Heart of the Matter.

Send mail to info@nemahealth.org with questions or comments about this web site.

Copyright © 1997 National Emergency Medicine Assoc., Inc.

Last modified: May 15, 1997

PENNSTATE



College of Medicine
University Hospital • Children's Hospital
The Milton S. Hershey Medical Center

Section of Trauma/Critical Care Surgery
J Stanley Smith, Jr., M.D., F.A.C.S., F.C.C.M.
Robert N. Cooney, M.D., F.A.C.S.
Peter Mochly, Jr., M.D., F.A.C.S.
Samuel B. Green, M.D., F.C.C.P.

Department of Surgery
The Milton S. Hershey Medical Center
The Pennsylvania State University
P.O. Box 850
Hershey, Pennsylvania 17033-0850
Telephone: (717) 531-4404
(717) 531-6241
Telefax: (717) 531-3649

June 18, 1997

Editor
Patriot News
PO Box 2265
Harrisburg, PA 17105

Dear Editor:

The Hershey Medical Center will be among forty major Trauma Centers across the country that will be evaluating a new treatment for critically injured patients with severe blood loss. The treatment involves administering an investigational blood product to those severely injured patients who face a major risk of dying despite the best medical care. Baxter Health Care Incorporated has developed the product Diaspirin Cross-linked Hemoglobin (DCLHb) which is being tested during the emergency treatment of these severely injured patients in shock. The trial which is authorized by the US Food and Drug Administration requires public notice because it will occur under emergency conditions that may require an "exception from informed consent". This letter will attempt to briefly describe the trial and ask for public comment.

The trial is being performed because these seriously injured patients frequently arrive at the hospital in shock with significant blood loss and have as high as a 40% chance of death. Previous studies performed in patients suggest that this new solution may improve the chance of survival for these victims. The product has the greatest chance of improving survival and reducing complications when it is given immediately after the beginning of shock and bleeding.

DCLHb is a purified hemoglobin preparation made from human blood that has become outdated in blood banks and no longer usable for transfusion. Hemoglobin is the red protein in the blood that carries oxygen. This solution is filtered and pasteurized to reduce the risk of any infection. DCLHb helps to restore blood pressure, increase blood flow to vital organs, and carry oxygen to cells and tissues much like regular blood. Blood typing is not required and the product can be stored for prolonged periods in the Emergency Department, so that it can be given immediately after a patient's arrival saving time in the stabilization of a trauma patient.

DCLHb does not replace the need for blood transfusion, but is administered in addition to regular blood. (Because it is a blood product, it is not suitable to treat patients whose religious beliefs forbid blood transfusions.) In this particular study, patients will get all the current best of standard therapy for their injuries including blood, other fluids and surgery. However, the DCLHb may reduce the number of blood transfusions needed to treat these injured patients.

DCLHb has been extensively studied in more than 700 patients over the past four years. There have been no dangerous side effects of the solution and patients that have received the solution may experience some harmless yellowing of the skin related to the metabolism of the protein as well as temporary reddening of the urine due to excretion of the protein in the urine. To further ensure patient safety, this national study will be monitored by a panel of independent experts with no relationship to the company or to any of the study centers.

The newest part of this particular study involves an "exception from informed consent in an emergency situation". Because these severely injured patients are often so badly injured, they may not be able to give their own consent to participate in such a study but are still in critical need of immediate treatment. Oftentimes, even families cannot be reached immediately after such injuries occur in order to give consent for their family member. Because these injuries are life threatening and the need to treat them is so critical and emergent, the US Food and Drug Administration has granted this particular study an "exception from informed consent" provided that the study centers follow careful guidelines. The FDA has carefully evaluated the DCLHb solution and determined that the potential benefits greatly outweigh the risks of participating in the trial.

As an institution, we will make every attempt to obtain consent from patients, their legal representatives or family before any DCLHb is given, and all patients and family members will be completely informed of their participation as soon as possible. At all times, the patients or their representatives may decline further participation in the study. There are no known risks to patients who decide not to continue in the study.

We at the University Hospital Trauma Center are excited about the potential that products such as DCLHb may have to not only save lives but also to extend the useful life of a very scarce resource: human blood. This product is an example of how innovations and treatment can expand the safety net and provide new therapies for victims of severe injuries.

We would welcome any public comment regarding this study, both positive and negative. Comments can be addressed to:

Dr. J Stanley Smith
Chief, Trauma Services
The Milton S. Hershey Medical Center
PO Box 850, Room C4804
Hershey, PA 17033

Sincerely,



J. Stanley Smith, Jr., MD, FACS, FCCM
Associate Professor of Surgery
Chief, Section of Trauma/Critical Care Surgery

JSS/cm



Handwritten notes: 5/11/97, 5/11/97

Section of Trauma/Critical Care Surgery
J. Stanley Smith, Jr., M.D., F.A.C.S., F.C.C.M.
Robert N. Cooney, M.D., F.A.C.S.
Peter Murchio, Jr., M.D., F.A.C.S.
Samuel Lee, Jr., M.D., F.C.C.P.

Department of Surgery
The Milton S. Hershey Medical Center
The Pennsylvania State University
P.O. Box 850
Hershey, Pennsylvania 17033-0850
Telephone: (717) 531-4301
(717) 531-6231
Telex: (717) 531-3649

June 18, 1997

Editor
Lebanon Daily News
718 Poplar Street
Lebanon, PA 17042

Dear Editor:

The Hershey Medical Center will be among forty major Trauma Centers across the country that will be evaluating a new treatment for critically injured patients with severe blood loss. The treatment involves administering an investigational blood product to those severely injured patients who face a major risk of dying despite the best medical care. Baxter Health Care Incorporated has developed the product Diaspirin Cross-linked Hemoglobin (DCLHb) which is being tested during the emergency treatment of these severely injured patients in shock. The trial which is authorized by the US Food and Drug Administration requires public notice because it will occur under emergency conditions that may require an "exception from informed consent". This letter will attempt to briefly describe the trial and ask for public comment.

The trial is being performed because these seriously injured patients frequently arrive at the hospital in shock with significant blood loss and have as high as a 40% chance of death. Previous studies performed in patients suggest that this new solution may improve the chance of survival for these victims. The product has the greatest chance of improving survival and reducing complications when it is given immediately after the beginning of shock and bleeding.

DCLHb is a purified hemoglobin preparation made from human blood that has become outdated in blood banks and no longer usable for transfusion. Hemoglobin is the red protein in the blood that carries oxygen. This solution is filtered and pasteurized to reduce the risk of any infection. DCLHb helps to restore blood pressure, increase blood flow to vital organs, and carry oxygen to cells and tissues much like regular blood. Blood typing is not required and the product can be stored for prolonged periods in the Emergency Department, so that it can be given immediately after a patient's arrival saving time in the stabilization of a trauma patient.

DCLHb does not replace the need for blood transfusion, but is administered in addition to regular blood. (Because it is a blood product, it is not suitable to treat patients whose religious beliefs forbid blood transfusions.) In this particular study, patients will get all the current best of standard therapy for their injuries including blood, other fluids and surgery. However, the DCLHb may reduce the number of blood transfusions needed to treat these injured patients.

DCLHb has been extensively studied in more than 700 patients over the past four years. There have been no dangerous side effects of the solution and patients that have received the solution may experience some harmless yellowing of the skin related to the metabolism of the protein as well as temporary reddening of the urine due to excretion of the protein in the urine. To further ensure patient safety, this national study will be monitored by a panel of independent experts with no relationship to the company or to any of the study centers.

The newest part of this particular study involves an "exception from informed consent in an emergency situation". Because these severely injured patients are often so badly injured, they may not be able to give their own consent to participate in such a study but are still in critical need of immediate treatment. Oftentimes, even families cannot be reached immediately after such injuries occur in order to give consent for their family member. Because these injuries are life threatening and the need to treat them is so critical and emergent, the US Food and Drug Administration has granted this particular study an "exception from informed consent" provided that the study centers follow careful guidelines. The FDA has carefully evaluated the DCLHb solution and determined that the potential benefits greatly outweigh the risks of participating in the trial.

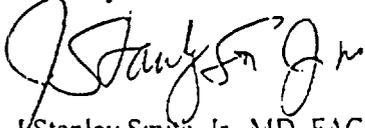
As an institution, we will make every attempt to obtain consent from patients, their legal representatives or family before any DCLHb is given, and all patients and family members will be completely informed of their participation as soon as possible. At all times, the patients or their representatives may decline further participation in the study. There are no known risks to patients who decide not to continue in the study.

We at the University Hospital Trauma Center are excited about the potential that products such as DCLHb may have to not only save lives but also to extend the useful life of a very scarce resource: human blood. This product is an example of how innovations and treatment can expand the safety net and provide new therapies for victims of severe injuries.

We would welcome any public comment regarding this study, both positive and negative. Comments can be addressed to:

Dr. J Stanley Smith
Chief, Trauma Services
The Milton S. Hershey Medical Center
PO Box 850, Room C4804
Hershey, PA 17033

Sincerely,



J. Stanley Smith, Jr., MD, FACS, FCCM
Associate Professor of Surgery
Chief, Section of Trauma/Critical Care Surgery

News**PENNSTATE****College of Medicine
University Hospital · Children's Hospital
The Milton S. Hershey Medical Center****FYI**P.O. Box 850
Hershey, Pennsylvania 17033
(717) 531-8606**FOR IMMEDIATE RELEASE
May 27, 1997****MEDIA INQUIRIES CONTACT:**
Leilyn Perri (o) (717) 531-8604
Deborah S. Saline (o) (717) 531-8606**NEW DRUG OFFERS NEW HOPE FOR TRAUMA PATIENTS**

HERSHEY, PA —Trauma-related injuries are the number one cause of death among Americans ages 1-45. For trauma patients at Penn State's Milton S. Hershey Medical Center, a new drug will be offered this summer that could greatly improve a patient's chance of survival.

"Only the most severely injured would be eligible for this study and right now 40 percent of these patients die as a result of their trauma. As an addition to all our best treatments, this new blood supplement quickly restores blood volume and increases blood pressure and the amount of oxygen in the blood. We hope we can reduce the number of deaths in this group by 25%," says Maggie Shand, R.N., CCRC, supervisor of clinical research for the department of surgery at the medical center.

The medical center is one of about 40 trauma centers nationwide that will be evaluating the use of the new blood supplement called Hemassist. An important part of this study involves a new guideline adopted by the Food and

- more -

An Equal Opportunity University

Page 2
BSUP

Drug Administration (FDA) waiving consent for studies in emergency situations. J Stanley Smith, M.D., chief of trauma services and associate professor of surgery at the medical center, says, "In many trauma cases patients are unconscious and families can't be located quickly enough for consent. Action must be taken in the first hour to save the patient's life. That is why this change by the FDA is so important." Shand says she does not anticipate problems with the consent waiver. She says she has heard of no problems at other centers around the country doing the study.

"These patients need help immediately. The response of the family is almost always supportive of whatever measures are needed to save the patient's life," Shand says.

The blood supplement is made from outdated blood that, in the past, would have been thrown out. Smith says a new filtration process allows the protein or hemoglobin to be extracted virtually virus-free from the outdated blood. This means the new blood supplement does not carry any risk of contamination. "We are getting the maximum use out of every drop of blood donated," says Smith.

Trauma surgeons at the medical center hope to begin using the blood supplement by the July 4th weekend. They say summer is the time when more trauma cases occur because more people tend to be traveling on the highways and there are more accidents. Smith says the blood supplement might be used in at least several cases per month at the medical center.

•BSUP•

Hershey Medical Center helps test blood substitute

BY DAVE BERGER
OF THE PATRIOT-NEWS

Hershey Medical Center will help test a blood substitute which, if found successful, could revolutionize emergency medicine and replenish the nation's limited supply of red blood cells.

The product, Baxter International's Diaspirin Cross-linked Hemoglobin, mimics the oxygen-carrying properties of red blood

Newly derived substance mimics traits characteristic to red cells, experts claim

cells. While it can't perform many of blood's important functions, it can carry oxygen to cells, increase blood flow to vital organs and restore patients' blood pressure.

Medical experts say it could prove invaluable in the treatment of severely injured patients.

"It probably will be viewed as a real breakthrough product," said Dr. Martha C. Farmer, director of technical communications for Baxter's Blood Substitutes Program, which manufactures the product known more commonly as DCLHb. "The last [comparable]

advance in treating trauma patients is probably the development of a good ambulance system."

The product has successfully completed two rounds of U.S. Food and Drug Administration-mandated tests. Next month, Hershey and 39 other trauma centers nationwide will begin using DCLHb in their emergency

See DIASPIRIN / Page B5

DIASPIRIN/Hershey Medical tests blood substitute

on Page B1

cy rooms as part of the final testing phase.

The hospitals will administer DCLHb to trauma patients who have lost at least 30 percent of their blood. Such patients suffer a 40 percent death rate, largely because their bodies cannot feed oxygen to their vital organs.

Trauma centers refer to the "golden hour" — within one hour of arrival at the emergency room — during which heavily bleeding trauma patients must receive blood transfusions. Patients' bodies will not accept a transfusion, however, unless it matches their blood type. Dr. Jay Smith, Hershey's chief of trauma services, said the search for a matching blood type can consume all of a patient's make-or-break hour.

Enter DCLHb. To make the new product, Baxter technicians penetrate the membranes of red blood cells and extract hemoglobin from within the cell. The cell's blood-type coding lies entirely in the membrane, so the

hemoglobin-based DCLHb has no specific blood type. Hence, it can be given to any patient, without a moment's delay.

DCLHb also lasts much longer than blood. Donated blood lasts only 42 days, so some of it goes to waste.

In contrast, DCLHb lasts as long as a year. When donated blood becomes outdated, technicians can remove the hemoglobin from the red cells and construct DCLHb, which stays for an additional year.

Doctors, pointing to the product's versatility, have set high goals for DCLHb.

"The first thing we want to achieve is to decrease the death rate" from 40 to 30 percent, Smith said. "Our second goal is to use less banked blood, because blood is in shorter and shorter supply. We would like to conserve a precious resource."

The nationwide testing will include 850 subjects, 20 of whom will go through Hershey. Following FDA guidelines, the trauma centers will treat half of the participants with DCLHb and the

other half — the control group — as usual.

Smith said the experimental treatment will add no health risk.

"They'll be getting blood also," he said. "This will be on top of everything else they would get — they don't get anything less."

Previous testing phases have shown DCLHb to be extremely safe; a 700-subject study, as well as earlier clinical studies, revealed no harmful side effects.

The product's sparkling record is especially important because many of the study participants will receive DCLHb without giving consent. Since DCLHb applies to emergency cases, the FDA granted Baxter a consent waiver for the product, allowing doctors to administer it immediately.

Baxter spokeswoman Mary Thomas said research "would not have been able to move forward" without the consent waiver, one of the first ever approved by FDA.

Hershey will still try to obtain

consent, Smith insisted, moving ahead only when an unconscious patient's relatives cannot be reached.

The study will continue at Hershey for approximately one year, after which the FDA will examine test results for an expected 12-18 months. If approved, DCLHb — which is also in its final testing stage in Europe — could become available in the U.S. as early as mid-1999.

PENNSTATE



INTERCOM

June 26, 1997

Intercom ONLINE at <http://www.psu.edu/INTERCOM/Home.html>

Volume 26, Number 34

Focus On

Research

Godley said.

Inter
June 26,

Hershey blood supplement should help trauma patients

Trauma-related injuries are the No. 1 cause of death among Americans ages 1-45. For trauma patients at The Milton S. Hershey Medical Center, a new blood supplement will be offered this summer that could greatly improve a patient's chance of survival.

"Only the most severely injured would be eligible for this study and right now 40 percent of these patients die as a result of their trauma. As an addition to all our best treatments, this new blood supplement quickly restores blood volume and increases blood pressure and the amount of oxygen in the blood. We hope we can reduce the number of deaths in this group by 25 percent," said Maggie Shand, a registered nurse and supervisor of clinical research for the department of surgery at the medical center.



The medical center is one of about 40 trauma centers nationwide that will be evaluating the use of the new blood supplement called Hemassist. An important part of this study involves a new guideline adopted by the Food and Drug Administration waiving consent for studies in emergency situations.

The blood supplement is made from outdated blood that, in the past, would have been thrown out. A new filtration process allows the protein or hemoglobin to be extracted virtually virus-free from the outdated blood. This means the new blood supplement does not carry any risk of contamination.

Trauma surgeons at the medical center hope to begin using the blood supplement by the July 4 weekend.

New treatment set for some trauma patients at HMC

HERSHEY - Trauma-related injuries are the number one cause of death among Americans ages 1-45. For trauma patients at the Hershey Medical Center, a new drug will be offered this summer that could greatly improve a patient's chance of survival.

"Only the most severely injured would be eligible for this study and right now 40 percent of these patients die as a result of their trauma. As an addition to all our best treatments, this new blood supplement quickly restores blood volume and increases blood pressure and the amount of oxygen in the blood. We hope we can reduce the number of deaths in this group by 25 percent," said Maggie Shand, R.N., CCRC, supervisor of clinical research for the department of surgery at the medical center.

The medical center is one of about 40 trauma centers nationwide that will be evaluating the use of the new blood supplement called Hemassist. An important part of the study involves a new guideline adopted by the Food and Drug Administration waiving consent for studies in emergency situations. J.

Stanley Smith, M.D., chief of trauma services and associate professor of surgery at the medical center, said, "In many trauma cases, patients are unconscious and families can't be located quickly enough for consent. Action must be taken in the first hour to save the patient's life. That is why this change by the FDA is so important."

Shand said she does not anticipate problems with the consent waiver. She said she has heard of no problems at other centers around the country doing the study.

"These patients need help immediately. The response of the family is almost always supportive of whatever measures are needed to save the patient's life," Shand said.

The blood supplement is made from outdated blood that in the past would have been thrown out. Smith said a new filtration process allows the protein or hemoglobin to be extracted virtually virus-free from the outdated blood. This means the new blood supplement does not carry any risk of contamination. "We are getting the maximum use out of

every drop of blood donated," Smith said.

Trauma surgeons at the medical center hope to begin using the blood supplement by the July 4 weekend. They said summer is the time when more trauma cases occur because more people tend to be traveling on the highways and there are more accidents. Smith said the blood supplement might be used in at least several cases per month at the medical center.

June 26, 1997.....Volume 26, Issue 34

Intercom

ONLINE

Penn State's faculty/staff newspaper

[News](#) . . . [Arts](#) . . . [Calendars](#) . . . [Letters](#) . . . [Links](#) . . . [Deadlines](#) . . . [Archive](#)

Search the contents of the *Intercom* archives and news releases issued by the Department of Public Information.

News and Features

- [Hershey/Geisinger merger date drawing near](#)
- [New promise for asthma sufferers](#)
- [Future look of University Park](#)
- [Going buggy](#)
- [Construction separates library wings](#)
- [Hershey exceeds national survival rates](#)
- [Professor earns \\$2 million grant](#)
- [WEB Browser](#)
- [Awards](#)
- [Intercollegiate Athletics](#)
- [Practice makes perfect](#)
- [Health plans must comply with new law](#)
- [Tuition legislation alert](#)
- [For the Record](#)
- [Penn State news bureau](#)
- [Lectures](#)
- [Central Pa. Festival of the Arts](#)
- [Special Olympics](#)
- [Promotions](#)
- [Book Shelf](#)
- [Parking fees](#)
- [News in Brief](#)
- [Continuous Quality Improvement](#)
- [Cool job](#)
- [Internal search](#)
- [Faculty/Staff Alerts](#)
- [More campaign leaders announced](#)
- [From the experts](#)
- [Research](#)

Continuous Quality Improvement

Strengthening the roster

The list of CQI teams formed at the University since the inception of quality improvement initiatives in 1991 continues to grow. A total of 232 teams have worked to improve processes over nearly six years. The newest teams include:

* The University Health Services General Medicine (GM) Department Patient Flow CQI Team was charged to study flow of patients in the General Medicine Department. The team's sponsor is **Larry Dansky** and the leader/facilitator is **Connie Cavalier**.

University of Pennsylvania.

The Penn Stater of the Quarter award recognizes, on a quarterly basis, a member of the DuBois campus family who has rendered particularly noteworthy service to the campus and/or the community.

Chemical engineering professor receives Fulbright

Jonathan Phillips, professor of chemical engineering, has been awarded a Fulbright grant to conduct research in the Department of Chemical Engineering at Ben-Gurion University in Israel. Phillips is an expert in heterogeneous catalysis. He is noted for a variety of discoveries, including discovering the mechanism of catalytic etching, an unexplained phenomenon for nearly a century.

Phillips is one of approximately 1,600 U.S. grantees who will travel abroad for the 1997-98 academic year under the Fulbright Program administered by the U.S. Information Agency. The Fulbright Program was established in 1946 by Congress to "increase mutual understanding between the people of the United States and the people of other countries."

[Back to top of page](#)

Research



Although many people feel more rushed now than ever, Geoffrey Godbey, professor of leisure studies, has found that Americans have roughly five hours more free time each week than they did in the 1960s.

Photo: Greg Grieco

How do Americans use their time?

By **Kimberley Yarnell Bierly**
Public Information

Though they may not believe it, Americans have more free time than they did 30 years ago. A researcher has shown that Americans have almost five hours more free time per week than in the 1960s.

"Most of the time they have gained is used for television viewing," said **Geoffrey Godbey**, professor of leisure studies in the College of Health and Human Development.

He and **John P. Robinson**, professor of sociology and director of the Americans' Use of Time Project at the University of Maryland, have conducted studies showing that the bigger issue is pace of life, because most of the free time comes during the week, but is in small amounts which don't allow a person to undertake more satisfying uses of leisure.

Their source of time-use information, the Americans' Use of Time Project, is the only such detailed historical data archive in the United States. Every 10 years the project has asked thousands of Americans to report their daily activities on an hour-by-hour basis in time diaries. These time diaries offer a more careful and complete account of where time goes because when the federal government measures work, they rely on people's estimates. The results of the time studies find that people are highly inaccurate in estimating their own work time.

Americans over 50 years old are the biggest gainers of free time, studies show. "People think they are working longer hours, but in reality, they mistake pace of work for length of time spent working. On average, the number of hours that people spend working has diminished," Godbey said.

On average, men and women have about the same amount of free time available to them.

Robinson and Godbey have described their findings in a new book, *Time For Life: The Surprising Ways Americans Use Their Time*, published by Penn State Press. They go beyond describing their controversial findings to confront the numerous time paradoxes facing Americans, such as feeling more rushed and stressed when we actually have more free time; having free time in periods when it is least useful; and investing time in activities that bring us minimal enjoyment or fulfillment.

Hershey blood supplement should help trauma patients

Trauma-related injuries are the No. 1 cause of death among Americans ages 1-45. For trauma patients at The Milton S. Hershey Medical Center, a new blood supplement will be offered this summer that could greatly improve a patient's chance of survival.

"Only the most severely injured would be eligible for this study and right now 40 percent of these patients die as a result of their trauma. As an addition to all our best treatments, this new blood supplement quickly restores blood volume and increases blood pressure and the amount of oxygen in the blood. We hope we can reduce the number of deaths in this group by 25 percent," said **Maggie Shand**, a registered nurse and supervisor of clinical research for the department of surgery at the medical center.



The medical center is one of about 40 trauma centers nationwide that will be evaluating the use of the new blood supplement called Hemassist. An important part of this study involves a new guideline adopted by the Food and Drug Administration waiving consent for studies in emergency situations.

The blood supplement is made from outdated blood that, in the past, would have been thrown out. A new filtration process allows the protein or hemoglobin to be extracted virtually virus-free from the outdated blood. This means the new blood supplement does not carry any risk of contamination.

Trauma surgeons at the medical center hope to begin using the blood supplement by the July 4 weekend.

[Back to top of page](#)

From the experts

Gardeners need to have proper tools for the job

Digging around in your garden is not exactly brain surgery, but like surgeons, every gardener should have the right tool for the right job.

Some may say that a shovel is just a shovel, but a scientist in the College of Agricultural Sciences said real gardeners need a spade -- and about four other essential gardening implements.

J. Robert Nuss, professor of ornamental horticulture, recommends five basic tools:

- * A long-handled spade. This tool is designed for digging with a straight blade set at an angle so it cuts easily into the soil.
- * A spading fork. This tool has flat, square tines and is used for moving heavy soil.
- * A steel rake. These large rakes are used to break up clay, smooth out soil and rake in fertilizers.
- * A hoe. Hoes are used to form rows, cover seeds, move soil, cut out weeds and make holes for planting seedlings.
- * A hand trowel. Hand tools are best for marking rows, weeding, making furrows and moving small plants, Nuss said.

Train your plants to survive indoors

Nuss also has tips to help your indoor garden thrive.

Most plants must be carefully prepared for the light conditions inside a building before placing them in a home, he said.

"If a plant doesn't receive enough light it will begin to use up its food reserves," Nuss said. "Without adequate light, plants will decline and then die."

Nuss said plants can be trained to accept lower levels of light by gradually reducing their light levels to the point that comes closest to an indoor environment. Depending on the plant, this could take up to 15 weeks.

Nuss recommends starting a plant in a sunny spot and then slowly moving it to areas of lesser light every few weeks.

"Once the plant has stabilized, you can provide the necessary light with incandescent or fluorescent lights," he said. But indoor light sources can give off a lot of heat, so don't put the light too close to the foliage.

FedEx USA Airbill

Tracking Number

5979301963

002632081 0

SPG12

Recipient's Copy

1 From
Date 10-10-97

Sender's Name Ellen Chiodo Phone (847) 270-3539
Dept./Floor/Suite/Room

Company BAXTER HEALTHCARE/W & SCI CTR

Address RTE 120 & WILSON RD

City ROUND LAKE State IL Zip 60073

2 Your Internal Billing Reference Information 296-711-156

3 To
Recipient's Name _____ Phone (301) 579-2012
Dept./Floor/Suite/Room

Company Food + Drug Administration

Address 12420 Parklawn Dr. Rm 1-23
(To "HOLD" at FedEx location, print FedEx address here)

City Rockville State MD Zip 20857

For HOLD at FedEx Location check here
 Hold Weekday (Not available with FedEx First Overnight)
 Hold Saturday (Not available with FedEx First Overnight or FedEx Standard Overnight)

For Saturday Delivery check here
 (Extra Charge. Not available at all locations) (Not available with FedEx First Overnight or FedEx Standard Overnight)



4a Express Package Service Packages under 150 lbs. Delivery commitment may be later in some areas.
 FedEx Priority Overnight (Next business morning) **FedEx Standard Overnight** (Next business afternoon) **FedEx 2Day*** (Second business day)
 NEW FedEx First Overnight (Earliest next business morning delivery to select locations) (Higher rates apply)
 20 EXP SAVER *FedEx Letter Rate not available. Minimum charge. One pound FedEx 2Day rate.

4b Express Freight Service Packages over 150 lbs. Delivery commitment may be later in some areas.
 FedEx Overnight Freight (Next business-day service for any distance) **FedEx 2Day Freight** (Second business-day service for any distance) **FedEx Express Saver Freight** (Up to 3 business-day service based upon distance)
(Call for delivery schedule. See back for detailed descriptions of freight products.)

5 Packaging **FedEx Letter** **FedEx Pak** **FedEx Box** **FedEx Tube** **Other Pkg.**
Declared value limit \$500

6 Special Handling
Does this shipment contain dangerous goods? Yes (As per attached Shipper's Declaration) Yes (Shipper's Declaration not required)
 Dry Ice (Dry Ice, & UN 1845 III x kg. 304 CA **Cargo Aircraft Only** (Dangerous Goods Shipper's Declaration not required)

7 Payment **Obtain Recipient FedEx Account No.**
Bill to: **Sender** (Account no. in section 1 will be billed) **Recipient** (Enter FedEx account no. or Credit Card no. below) **Third Party** **Credit Card** **Cash/Check**



Total Packages 2 Total Weight 2 Total Declared Value* \$ - 0 - 00 Total Charges
When declaring a value higher than \$100 per shipment, you pay an additional charge. See SERVICE CONDITIONS, DECLARED VALUE AND LIMIT OF LIABILITY section for further information. Credit Card Auth.

8 Release Signature

Your signature authorizes Federal Express to deliver this shipment without obtaining a signature and agrees to indemnify and hold harmless Federal Express from any resulting claims.

Questions?
Call 1-800-Go-FedEx
(1-800-463-3339)

272

Rev. Date 6/95
PART #147556
©1994-95 FedEx
PRINTED IN U.S.A.
GAF 6/97

002632081 0

3
2004
CNCU
LT. GRAY/GRIS/GRIS CLAR