

Section 4

Community Consultations

Surgical Grand Rounds

Community Meeting #1

Community Meeting #2

(Handouts, Power Point Presentation)

Leadership 2015 technology Day

(With Feedback)

Postcard Distribution at Local Mall

(With Feedback)



ETSU SURGICAL
GRAND ROUNDS

*“PolyHeme, A Novel Blood
Substitute”*

Julie Dunn, M.D.
Department of Surgery
East Tennessee State University

October 29, 2004
12 Noon
Women’s Center Conference Room
Johnson City Medical Center

AGENDA FOR COMMUNITY MEETING

Washington County EMS Headquarters
November 4, 2004
AGENDA

POLYHEME® TRAUMA TRIAL COMMUNITY MEETING

A Phase III, Randomized, Controlled, Open-Label Multicenter, Parallel Group Study Using Provisions for Exception from Informed Consent Requirements Designed to Evaluate the Safety and Efficacy of Poly SFH-P Injection [Polymerized Human Hemoglobin (Pyridoxylated) PolyHeme®] When Used to Treat Patients in Hemorrhagic Shock Following Traumatic Injuries Beginning in the Prehospital Setting

7:00 pm	Refreshments and Registration	
7:15 pm	Welcome and Introductions	James Watson Andrea Hyde, RN, BSN
7:20 pm	Federal regulations and the IRB	Dr. Dunn
7:30 pm	Explanation of PolyHeme® trial	Dr. Dunn
7:45 pm	Questions and Answers	Dr. Dunn
8:30 pm	Adjourn	

Handouts are available at the back of the room.

AGENDA FOR COMMUNITY MEETING

Jonesborough Public Library
January 4, 2005
AGENDA

POLYHEME® TRAUMA TRIAL COMMUNITY MEETING

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- 6:00 pm Refreshments and Registration
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- 6:20 pm Federal regulations and the IRB
- 6:30 pm Explanation of PolyHeme® trial
- 6:45 pm Questions and Answers
- 7:15 pm Adjourn

Handouts are available at the back of the room.

FEEDBACK FORM FOR PARTICIPANTS

Community Consultation
Washington County EMS Headquarters
November 4, 2004

Please circle your answers

1. Would you support a study such as the one described at this meeting being conducted in this community, specifically, a study in which severely injured and bleeding patients would be enrolled without giving their informed consent?

Yes No

2. If you were severely injured and bleeding and were being treated by the paramedics in your community, would you want to be enrolled in this type of study?

Yes No

3. If a family member of yours were severely injured and bleeding and were to be treated by the paramedics, would you want him or her to be enrolled in this type of study?

Yes No

4. Do you have any comments or concerns you wish to share with the investigators?

Age: _____ Ethnic background: _____

Gender: Male _____ Female _____

Thank you for your participation today.
Please call Andrea Hyde, RN, BSN at 423-439-7313 if you have any other questions.

PolyHeme® Backgrounder

PolyHeme® Characteristics

PolyHeme® is a unique human hemoglobin-based oxygen-carrying blood substitute in development for the treatment of urgent, large volume blood loss in trauma and surgical settings, with a particular focus on settings where blood is not immediately available.

PolyHeme® is the only blood substitute in development that has been rapidly and safely infused in clinical trials in sufficiently massive quantities to be useful in the treatment of urgent, large volume blood loss. PolyHeme's unique characteristics make it the ideal resuscitative fluid:

- Simultaneously restores lost blood volume and hemoglobin levels
- Is universally compatible (does not need to be typed or cross-matched before infusion)
- Is immediately available
- Supports life in the absence of red blood cells (RBCs)
- Reduces risk of disease transmission
- Does not cause transfusion reactions
- Allows rapid, massive infusion
- Has extended shelf life of over 12 months
- Is manufactured from human blood
- Has been used to treat more than 300 patients in five clinical trials.
- Favorable safety profile. No clinically significant drug-related adverse effects, specifically, no organ toxicities nor systemic or pulmonary hypertension have occurred in clinical trials to date
- In a trial of 171 trauma patients in the hospital setting, PolyHeme® significantly improved survival compared to historical controls who did not receive blood

Potential Uses for PolyHeme®

The clinical need for a safe and effective resuscitative fluid and blood substitute when blood is not available is recognized by both civilian and military trauma surgeons throughout the world. Blood may not be immediately available in the following situations:

- At the scene of injury or disaster in civilian or military settings
- During transport to the hospital via ground or air ambulance
- Upon arrival in the hospital before typing and cross-matching can be accomplished
- In the operating room in the case of unplanned surgical hemorrhage
- In remote or rural settings, including hospitals, where blood may be in limited supply
- In situations where the needs of multiple, simultaneously injured patients may overwhelm a hospital's inventory of stored blood
- In cases of inventory imbalance
- In cases of incompatibility
- In cases of religious objection
- On the battlefield

Northfield Laboratories History

Northfield Laboratories was established as a company in 1985. However, the scientific founders of Northfield began working on the development of PolyHeme® as an academic research project in 1969. At that time, the U.S. Army provided research funding to develop a blood substitute that met its criteria for utility in battlefield settings.

Northfield has always used human blood as its starting material, believing this is the most desirable starting material. PolyHeme® is derived by lysing the red blood cells in outdated human blood and extracting the tetrameric hemoglobin protein which carries oxygen from inside. Northfield's unique proprietary technology involves a chemical modification to the native hemoglobin that results in a polymerized hemoglobin molecule.

The early development of hemoglobin-based oxygen carriers (HBOCs) was problematic. Early preparations of unmodified tetrameric hemoglobin were plagued by renal, hepatic, gastrointestinal, pancreatic, and cardiovascular toxicities and resulting organ dysfunction. The small molecular-weight tetrameric species of hemoglobin have been implicated as causative agents associated with these unacceptable adverse effects. Even contemporary preparations with modified tetrameric hemoglobin have demonstrated similar evidence of such toxicities. The basis of these adverse effects has been attributed to vasoconstriction due to the small molecular-weight tetramers. The preparation of PolyHeme®, however, is designed to avoid these toxicities by removing essentially all vasoactive tetramer through high-yield polymerization and subsequent filtration to purify the solution and result in larger polymerized molecules.

Northfield has extensive experience with PolyHeme® in critically injured trauma patients, including those who have received up to 20 units or 1,000 gm of PolyHeme®. Since the normal volume of blood in a human is 10 units or 500 gm, this signifies up to 2 times the normal volume of blood in a human has been replaced successfully by PolyHeme®. Northfield has published its data showing the life-saving capability in humans following such massive blood loss, in which patients have lost virtually all of their own blood. The study was published in a manuscript entitled *The Life-Sustaining Capacity of Human Polymerized Hemoglobin when Red Cells Might Be Unavailable*, in the Journal of the American College of Surgeons in October 2002.

Civilian Ambulance Trial

Northfield is currently enrolling patients in a landmark Phase III pivotal trial using PolyHeme® starting in the prehospital setting in the field and ambulance. The trial is designed to lead to the licensure of PolyHeme® for use in trauma in both civilian and military settings. Northfield anticipates the trial will take approximately one year when underway and is hopeful that patient enrollment will begin in the late spring or early summer. Key aspects of this trial include:

- The only trial of a blood substitute in the U.S. to be conducted in the prehospital setting
- The trial will be conducted in 15-20 Level I trauma centers throughout the U.S.
- It is expected that 720 patients will be enrolled in the trial.
- The primary endpoint of the trial is survival

In the civilian environment, blood is not commonly used in the field or during ambulance transport to the hospital. The current approach to resuscitation of the trauma victim begins with the rapid infusion of salt water solution, which does not carry oxygen. PolyHeme® is a good volume replacement in lieu of salt water, and also provides immediate and universally compatible oxygen-carrying capacity.

The second stage of resuscitation is to infuse blood or red blood cells (RBCs) when they become available. In the hospital, it takes approximately 45 minutes to one hour to obtain fully cross-matched compatible blood. PolyHeme® can eliminate this delay. Therefore, PolyHeme® may represent a single initial fluid to restore both lost volume and lost oxygen-carrying capacity due to blood loss that may fundamentally alter the early care of the injured patient.

Summary

The development of PolyHeme® has progressed to the initiation of a landmark civilian ambulance trial based on the results of extensive clinical experience in critically injured trauma patients. Successful completion of this trial should lead to the licensure of PolyHeme® for use in trauma in both civilian and military settings where blood is not immediately available.

§ 50.24 Exception from informed consent requirements for emergency research.

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

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
2. Obtaining informed consent is not feasible because:
 - i. The subjects will not be able to give their informed consent as a result of their medical condition;
 - ii. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
 - iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
3. Participation in the research holds out the prospect of direct benefit to the subjects because:
 - i. Subjects are facing a life-threatening situation that necessitates intervention;
 - ii. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 - iii. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
4. The clinical investigation could not practicably be carried out without the waiver.
5. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with § 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.
7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
 - i. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
 - ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
 - iii. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

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

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

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

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §§ 312.30 or 812.35 of this chapter.

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

HISTORY:

[61 FR 51498, 51528, Oct. 2, 1996]

1 PolyHeme®
Trauma Trial
Community Consultation

Hospital Name
Hospital Website
Location
Date

2 Clinical Investigator
• [Doctor's name, credentials, and contact info]

- 3 Study Sponsor
Northfield Laboratories Inc.
- Developer of the oxygen-carrying blood substitute called PolyHeme®
 - Conducted multiple studies with PolyHeme over the past decade
 - Most studies have been with injured trauma patients
 - Company website: www.northfieldlabs.com

4 Study Purpose

*To evaluate the life-saving potential of PolyHeme®
when given to severely injured and bleeding patients in
"hemorrhagic shock," starting at the scene of injury*

5 What is Hemorrhagic Shock?

Hemorrhagic: massive loss of blood

Shock: life-threatening condition

- Dangerously low blood pressure
- Internal organs don't receive enough oxygen and have difficulty functioning
- Might lead to death

6 Need for Improved Outcome

- The Center for Disease Control (CDC) lists trauma as the leading cause of death among Americans under age 45
- Thousands of trauma patients die each year
- Many of these patients die because the "standard of care" cannot reverse the damaging effects of hemorrhagic shock

7 What is the Standard of Care?

Represents the current treatment

8 Standard of Care Limitations

In the Ambulance

- Salt water does not carry oxygen, unlike blood
- Without enough oxygen, the body and its internal organs have difficulty functioning and can stop working (organ failure)

9 Standard of Care Limitations

In the Hospital

- Donated blood takes time (45-60 minutes) to be matched for each patient
- Patients who receive more than 6 units of donated blood in the first 12 hours have an increased risk of organ failure

10 What is PolyHeme®?

*A blood substitute
that carries oxygen*

1 unit of PolyHeme

=

1 unit of blood

11 What is PolyHeme®?

- Made from human blood
- Compatible with all blood types
- Immediately available
- Reduced risk of viral disease (viral load reduced over a billion times)

12 Why Use PolyHeme®?

- PolyHeme was developed to treat blood loss when blood is not available
 - Blood is not available in the ambulance
 - PolyHeme will be immediately available in the ambulance and carries oxygen
- PolyHeme can reduce the use of donated blood in the first 12 hours after injury, and might avoid potential organ failure

13 Why Use PolyHeme®?

*To improve survival
patients*

of severely injured and bleeding

14 PolyHeme® Experience

- PolyHeme has been studied in more than 300 individuals and 5 different clinical

trials

- PolyHeme has been extensively studied in hospitalized trauma patients
- *PolyHeme has kept trauma patients alive when they have lost all of their own blood*

15 PolyHeme® Experience

Past studies have shown that PolyHeme

- Carries as much oxygen as blood (1 unit of PolyHeme = 1 unit of blood)
- Reduces need for donated blood
- Has not caused organ damage
- Has replaced up to two times a person's entire blood volume (2 x 10 units = 20 units)

16 Trial Design: Before the Hospital

Severely injured trauma patients will be assigned to either one of two groups by chance

Control Test

Receive salt water

17 Ambulance Infusion

18 Trial Design: At the Hospital

1 *Control*

- Salt water for hydration
- Donated blood to boost oxygen levels

2 *Test*

- Salt water for hydration
- PolyHeme® to boost oxygen levels
- Maximum dose of 6 units during first 12 hours
- Donated blood will be used thereafter

19 Hospital Infusion

20 Who Would Be Included?

Patients at risk of dying

- Who have sustained severe injuries
- Who have lost a large amount of blood and are in shock
- Who are at least 18 years old
- Who are of either gender (male or female)

21 Who Would Be Excluded?

- 1
- Patients who are obviously pregnant
 - Patients who have severe head or brain injuries
 - Patients who have "unsurvivable" injuries

- 2 • Patients who require CPR
- Patients with known objections to blood transfusions
- Patients with known orders not to resuscitate

22 FDA Review

- Northfield Laboratories received clearance to proceed with this study from the Food and Drug Administration (FDA)
- The FDA authorized the use of an exception from informed consent requirements for this study

23 What is Informed Consent?

A process by which patients make informed decisions about participating in research studies

- Traditionally required for all research studies
- Research studies compare 2 treatments (standard vs. investigational)
- Doctors describe each of these potential treatments

24 What is Informed Consent?

A process by which patients make informed decisions about participating in research studies

- Patients are informed of the potential risks and potential benefits associated with each of these treatments
- Patients choose whether to participate in the study

25 What is Exception from Informed Consent?

Patients are enrolled in a research study without giving their informed consent

26 How Can That Be?

A federal regulation (21 CFR 50.24), created in 1996, allows certain studies that meet the following criteria to use this exception

- *Patients' lives must be at risk*
- Available treatments are not satisfactory
- Patients are unable to give consent
- Potential risks are reasonable

27 How Can That Be?

A federal regulation (21 CFR 50.24), created in 1996, allows certain studies that meet the

following criteria to use this exception

- Participation in the research could provide a direct benefit (*increased survival*) to the patient
- The research could not be practicably carried out without an exemption

28 Consent Safeguards

- If possible, the patient or a legally authorized representative (LAR) can give consent before the patient is enrolled in the study
- If consent cannot be obtained before enrollment, frequent attempts will be made to contact the patient's LAR and family to describe the study

29 Consent Safeguards

The patient, family members, or a legally authorized representative may decide to withdraw the patient at any time

30 Potential Benefits of PolyHeme®

- *Might increase the likelihood of survival*
- Can enhance the amount of vital oxygen in the patient's blood
- Is compatible with all blood types
- Is immediately available
- Has reduced risk of viral disease
(viral load reduced over a billion times)

31 Potential Risks of PolyHeme®

- Rash
- Increased blood pressure
- Kidney or liver damage
- Viral infection (HIV, hepatitis, etc.)
- Unforeseen happenings

32 Patient Protection

The Institutional Review Board (IRB) is a group of medical, scientific, and nonscientific members of the community

- Reviews all proposals for research on humans
- Assures patient safety
- Monitors community feedback

33 Patient Protection

- The IRB will decide whether or not to allow this hospital to participate in the PolyHeme® trial
- An independent data monitoring committee will oversee the trial
- The FDA will be kept informed of the trial's progress

34 If We Participate...

- The results of the study will be revealed to the community after the trial has been completed
- Those who do not want to participate in the study can [wear a special bracelet] to exclude themselves

35 Questions or Comments?

QUESTIONS AND ANSWERS POLYHEME® TRAUMA TRIAL

Why is this study being conducted?

To evaluate the safety and efficacy of PolyHeme® in treating severely injured and bleeding patients, starting at the scene of injury, and to assess a potential survival benefit.

What is the title of this study?

A Phase III, Randomized, Controlled, Open-Label, Multicenter, Parallel Group Study Using Provisions for Exception from Informed Consent Requirements Designed to Evaluate the Safety and Efficacy of Poly SFH-P Injection [Polymerized Human Hemoglobin (Pyridoxylated) PolyHeme®] When Used to Treat Patients in Hemorrhagic Shock Following Traumatic Injuries Beginning in the Prehospital Setting

What is the design of this study?

Patients in “hemorrhagic shock” will begin to receive either saline (salt water), which is the standard of care (control), or PolyHeme (investigational treatment). Treatment would begin before arrival at the hospital, either at the scene of the injury or in the ambulance, and continue during a 12 hour postinjury period in the hospital.

In the hospital, patients in the control group will receive saline for hydration and blood if necessary to boost oxygen levels. Unlimited doses of each are allowed.

Patients in the treatment group will receive saline (salt water) for hydration and PolyHeme® to boost oxygen levels if necessary. The maximum dose of PolyHeme will be 6 units during the first 12 hours. Blood will be used thereafter.

What is hemorrhagic shock?

A condition in which a patient has experienced massive blood loss. Shock is a life-threatening condition that might include:

- *Dangerously low blood pressure*
- *Internal organs not receiving enough oxygen and have difficulty functioning, which could lead to death*

Why is there a need for improvement in the way trauma patients are treated now?

Trauma is the leading cause of death among Americans under the age of 45. Currently the only available treatment for hemorrhagic shock, when blood is not available, is the infusion of a solution such as saline, which does not carry oxygen. Therefore, when

blood is not immediately available, use of an oxygen carrier such as PolyHeme may restore sufficient circulating levels of hemoglobin and potentially improve patient survival.

What is the current standard of care? How are trauma patients usually treated?

Patients are given a solution such as saline at the scene or in the ambulance. When they arrive at the hospital, they are given blood after typing and cross-matching is accomplished.

Who would be eligible for the study?

*Patients who have lost a large amount of blood and are in shock
Patients who are at least 18 years old
Patients who have sustained severe injuries*

Who would be excluded from the study?

*Women who are obviously pregnant
Patients with severe brain injuries
Patients who require CPR to maintain their heartbeat
Patients with “unsurvivable” injuries
Patients who are known to object to blood transfusions
Patients who are known to refuse resuscitation*

What is PolyHeme®?

PolyHeme® is an oxygen-carrying blood substitute made from human blood. PolyHeme® requires no cross-matching, and therefore is compatible with all blood types. It could provide immediate therapy when blood is not available. PolyHeme® is highly purified to reduce the risk of viral disease transmission. It has a shelf-life of over 12 months.

Has PolyHeme® been tested on humans before?

There have been 5 human clinical trials of PolyHeme®.

The observations in these trials have demonstrated the potential usefulness of PolyHeme in the treatment of urgent blood loss and life-threatening hemoglobin levels. In these trials of hospitalized patients, PolyHeme significantly improved survival compared to historical control patients who did not receive blood. Our trials have involved high dosage and rapid infusion of PolyHeme in situations that are life-threatening and where massive blood loss routinely occurs.

How many patients have been treated with PolyHeme®?

Over 300 patients have been treated, including patients in a hospital-based trauma trial.

What is known about the safety of PolyHeme®?

PolyHeme® has been demonstrated to be well tolerated in the patient populations tested in clinical trials to date.

What is an exception from informed consent?

Patients are enrolled in a clinical study without giving informed consent before being enrolled.

Why was such an exception granted in connection with this study?

Patients are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of particular interventions.

Participating in the study has the potential for of direct benefit to the enrolled patients, defined as an increase in survival, because:

- Patients are in a life-threatening situation that necessitates intervention*
- Previous studies support the potential to provide a direct benefit to enrolled patients*
- Risks associated with the use of the PolyHeme® are reasonable in relation to what is known about the patients' medical condition, the risks and benefits of standard therapy, and the risks and benefits of the proposed intervention*

It is expected that patients will be unable to give informed consent because the extent of their injuries and the fact that they are in shock.

It is unlikely that there will be time to find and ask for consent from the patient's legally authorized representative (LAR) or to provide an opportunity for a family member to object to the patient's enrollment before beginning treatment.

Who grants such exceptions?

The U.S. Food and Drug Administration (FDA) under regulations called 21 Code of Federal Regulations 50.24 specifies the conditions under which an exception from informed consent may be obtained. The Institutional Review Board (IRB) associated with each hospital approves its use locally.

What if patients don't want to participate in this study?

Patients can withdraw from the study, without prejudice, at any time by notifying the investigator.

Will patients still receive treatment if they don't want to participate in the study?

Patients will still receive the standard of care if they decline to participate in this study.

What are the potential benefits of participating in the study?

PolyHeme® may increase the likelihood of survival after traumatic injury

The need for blood transfusion might be reduced

Patients might avoid a reduction in the function of internal organs that sometimes follows blood transfusion.

What are the potential risks of participating in the study?

Rash

Increased blood pressure

Kidney or liver damage

Transmission of hepatitis and HIV viruses

Unforeseen happenings

How much will it cost patients to participate?

There is no charge to the patient to participate in this study. The costs of certain laboratory tests that are required will be paid by the study sponsor.

Will patients get paid to participate?

No, patients will not be paid to participate in this study.

Who is the manufacturer of PolyHeme®?

Northfield Laboratories Inc., Evanston, IL. For more information, visit www.northfieldlabs.com

FEEDBACK FORM FOR PARTICIPANTS

Community Consultation
Washington County EMS Headquarters
November 4, 2004

Please circle your answers

1. Would you support a study such as the one described at this meeting being conducted in this community, specifically, a study in which severely injured and bleeding patients would be enrolled without giving their informed consent?

Yes No

2. If you were severely injured and bleeding and were being treated by the paramedics in your community, would you want to be enrolled in this type of study?

Yes No

3. If a family member of yours were severely injured and bleeding and were to be treated by the paramedics, would you want him or her to be enrolled in this type of study?

Yes No

4. Do you have any comments or concerns you wish to share with the investigators?

Age: _____ Ethnic background: _____

Gender: Male _____ Female _____

Thank you for your participation today.
Please call Andrea Hyde, RN, BSN at 423-439-7313 if you have any other questions.

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- Simultaneously restores lost blood volume and hemoglobin levels
- Is universally compatible (does not need to be typed or cross-matched before infusion)
- Is immediately available
- Supports life in the absence of red blood cells (RBCs)
- Reduces risk of disease transmission
- Does not cause transfusion reactions
- Allows rapid, massive infusion
- Has extended shelf life of over 12 months
- Is manufactured from human blood
- Has been used to treat more than 300 patients in five clinical trials.
- Favorable safety profile. No clinically significant drug-related adverse effects, specifically, no organ toxicities nor systemic or pulmonary hypertension have occurred in clinical trials to date
- In a trial of 171 trauma patients in the hospital setting, PolyHeme® significantly improved survival compared to historical controls who did not receive blood

Potential Uses for PolyHeme®

The clinical need for a safe and effective resuscitative fluid and blood substitute when blood is not available is recognized by both civilian and military trauma surgeons throughout the world. Blood may not be immediately available in the following situations:

- At the scene of injury or disaster in civilian or military settings
- During transport to the hospital via ground or air ambulance
- Upon arrival in the hospital before typing and cross-matching can be accomplished
- In the operating room in the case of unplanned surgical hemorrhage
- In remote or rural settings, including hospitals, where blood may be in limited supply
- In situations where the needs of multiple, simultaneously injured patients may overwhelm a hospital's inventory of stored blood
- In cases of inventory imbalance
- In cases of incompatibility
- In cases of religious objection
- On the battlefield

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Northfield has always used human blood as its starting material, believing this is the most desirable starting material. PolyHeme® is derived by lysing the red blood cells in outdated human blood and extracting the tetrameric hemoglobin protein which carries oxygen from inside. Northfield's unique proprietary technology involves a chemical modification to the native hemoglobin that results in a polymerized hemoglobin molecule.

The early development of hemoglobin-based oxygen carriers (HBOCs) was problematic. Early preparations of unmodified tetrameric hemoglobin were plagued by renal, hepatic, gastrointestinal, pancreatic, and cardiovascular toxicities and resulting organ dysfunction. The small molecular-weight tetrameric species of hemoglobin have been implicated as causative agents associated with these unacceptable adverse effects. Even contemporary preparations with modified tetrameric hemoglobin have demonstrated similar evidence of such toxicities. The basis of these adverse effects has been attributed to vasoconstriction due to the small molecular-weight tetramers. The preparation of PolyHeme®, however, is designed to avoid these toxicities by removing essentially all vasoactive tetramer through high-yield polymerization and subsequent filtration to purify the solution and result in larger polymerized molecules.

Northfield has extensive experience with PolyHeme® in critically injured trauma patients, including those who have received up to 20 units or 1,000 gm of PolyHeme®. Since the normal volume of blood in a human is 10 units or 500 gm, this signifies up to 2 times the normal volume of blood in a human has been replaced successfully by PolyHeme®. Northfield has published its data showing the life-saving capability in humans following such massive blood loss, in which patients have lost virtually all of their own blood. The study was published in a manuscript entitled *The Life-Sustaining Capacity of Human Polymerized Hemoglobin when Red Cells Might Be Unavailable*, in the Journal of the American College of Surgeons in October 2002.

Civilian Ambulance Trial

Northfield is currently enrolling patients in a landmark Phase III pivotal trial using PolyHeme® starting in the prehospital setting in the field and ambulance. The trial is designed to lead to the licensure of PolyHeme® for use in trauma in both civilian and military settings. Northfield anticipates the trial will take approximately one year when underway and is hopeful that patient enrollment will begin in the late spring or early summer. Key aspects of this trial include:

- The only trial of a blood substitute in the U.S. to be conducted in the prehospital setting
- The trial will be conducted in 15-20 Level I trauma centers throughout the U.S.
- It is expected that 720 patients will be enrolled in the trial.
- The primary endpoint of the trial is survival

In the civilian environment, blood is not commonly used in the field or during ambulance transport to the hospital. The current approach to resuscitation of the trauma victim begins with the rapid infusion of salt water solution, which does not carry oxygen. PolyHeme® is a good volume replacement in lieu of salt water, and also provides immediate and universally compatible oxygen-carrying capacity.

The second stage of resuscitation is to infuse blood or red blood cells (RBCs) when they become available. In the hospital, it takes approximately 45 minutes to one hour to obtain fully cross-matched compatible blood. PolyHeme® can eliminate this delay. Therefore, PolyHeme® may represent a single initial fluid to restore both lost volume and lost oxygen-carrying capacity due to blood loss that may fundamentally alter the early care of the injured patient.

Summary

The development of PolyHeme® has progressed to the initiation of a landmark civilian ambulance trial based on the results of extensive clinical experience in critically injured trauma patients. Successful completion of this trial should lead to the licensure of PolyHeme® for use in trauma in both civilian and military settings where blood is not immediately available.

§ 50.24 Exception from informed consent requirements for emergency research.

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

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
2. Obtaining informed consent is not feasible because:
 - i. The subjects will not be able to give their informed consent as a result of their medical condition;
 - ii. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
 - iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
3. Participation in the research holds out the prospect of direct benefit to the subjects because:
 - i. Subjects are facing a life-threatening situation that necessitates intervention;
 - ii. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 - iii. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
4. The clinical investigation could not practicably be carried out without the waiver.
5. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with § 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.
7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
 - i. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
 - ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
 - iii. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

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

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

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

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §§ 312.30 or 812.35 of this chapter.

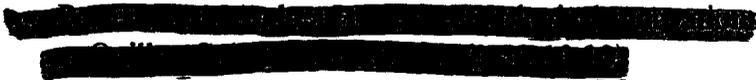
(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly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

HISTORY:

[61 FR 51498, 51528, Oct. 2, 1996]

Leadership 2015 Technology Day January 20, 2005

The goal of the technology day for 2005 is to make the leadership group aware of the fascinating and exciting endeavors already taking place in the community that revolve around technology. Today's event explores information technology, biotechnology, and nanotechnology.

Time	Location
7:45 AM	Departure from City Hall
8:00 – 9:30	Millennium Center <ul style="list-style-type: none">• Continental Breakfast (8:00-8:15)• Welcome, Tim Seeberg, Millennium Center (8:15-8:30)• Presentation, Russ Davis, Landmark GIS (8:30-8:45)• Presentation, Mark Stribling, Orison (8:45-9:00)• 10 minute break• Presentation, Shannon McCool, Fallon Group (9:10-9:25)• Questions (9:30)
9:45 – 11:15	Quillen College of Business Meet in lobby of Stanton-Gerber Hall Host is Dr. Michael Woodruff  <ul style="list-style-type: none">• 10 minute break (10:10-10:20)• Presentation, Dave Williams, Technological Innovations at Quillen College of Medicine (10:20-10:40)• Patient simulator demonstration/facility tour (10:40-11:15)
11:30 – 1:00	ETSU Innovation Lab <ul style="list-style-type: none">• Tour Innovation Lab by Dave Lawrence (11:30-12:00)• Lunch sponsored by Med Tech Park (12:00-1:00)• Presentation by Elisa Comer, ELTS (12:10-12:20)• Presentation by Andreas Papas, Yasoo Health (12:20-12:30)• Presentation, Dr. Michael Woodruff. He will discuss the University's role in creating a research foundation and

the importance to the region's ability to grow technology companies (12:30-1:00)

1:15 – 2:30

Siemens Electronic Manufacturing Center

- Presentation on manufacturing technology by Louise Stump Plant Manager (1:15-1:45)
- Split into four groups for plant tour (1:45-2:30)

2:45 – 3:45

NTARA

- Tour on NTARA facility (2:45-3:15)
- Presentation, Jeff Morris and Tony Baldwin, NTARA's evolution and new business model (3:15-3:45)

4:00 PM

Return to City Hall

Community Consultation and Public Disclosure Feedback:

Attached is the Feedback form for participants from 1-20-2005

This includes 13 responses from approximately 30 attendees representing 43%.

The 13 responses breakdown:

100% Caucasian

8 Male

5 Female

36.5 the average age with 29 youngest and 52 highest and one not reporting age.

100 % stated they would support the PolyHeme Study with regards to the exclusion from informed consent issue.

92% stated that they would want to be enrolled in the study if they were severely injured or bleeding.

85% stated they would want their family member to be enrolled in the study if they were injured or severely bleeding. (7% said no 7% were undecided)

FEEDBACK FORM FOR PARTICIPANTS

Community Consultation
Leadership 2015 Technology Day
January 20, 2005

Please circle your answers

1. Would you support a study such as the one described at this meeting being conducted in this community, specifically, a study in which severely injured and bleeding patients would be enrolled without giving their informed consent?

Yes 13 No 0

2. If you were severely injured and bleeding and were being treated by the paramedics in your community, would you want to be enrolled in this type of study?

Yes 12 No 1

3. If a family member of yours were severely injured and bleeding and were to be treated by the paramedics, would you want him or her to be enrolled in this type of study?

Yes 11 No 1 Undecided 1 Choice is important . . . can't really say.

4. Do you have any comments or concerns you wish to share with the investigators?

* I am concerned about only providing a 30 day f/u after use of the drug.

*The risks were not fully discussed or addressed.

*Sounds like a fascinating project.

*Program could use more PR and marketing w/ groups like this. This is very exciting and we should be proud to have it at ETSU/Med.School.

Average age: 36.5 Ethnic background: Caucasian 13

Gender: Male 8 Female 5

Thank you for your participation today.
Please call Andrea Hyde at 423-439-7313 if you have any other questions.

YOUR OPINION MATTERS TO US.



Postage
Required
Post Office will
not deliver
without proper
postage.

**ATTN: ANDREA HYDE RN
ETSU POLYHEME STUDY
325 N STATE OF FRANKLIN RD THIRD FLOOR
JOHNSON CITY TN 37604-6062**



East Tennessee State University and Johnson City – Washington County EMS will join Johnson City Medical Center, one of a select number of trauma centers in the U.S. chosen to participate in a national clinical research study to evaluate the safety and effectiveness of PolyHeme®, an oxygen-carrying blood substitute, in treating critically injured and bleeding patients. Under the study protocol, treatment would begin before arrival at the hospital, either at the scene of the injury or in the ambulance, and continue for 12 hours. Since blood is not presently carried in ground ambulances, the use of PolyHeme in this setting could address an unmet medical need for an oxygen-carrying solution where blood is currently not available.

The U.S. Food and Drug Administration allows for certain studies to be performed without consent in emergency settings but only if patients have a high risk of dying without treatment, cannot communicate because of their illnesses, and do not have a legally authorized representative available to speak for them. When there is no other known treatment available to improve their chances of survival, patients may be given an experimental agent but only if it has been approved in advance by an independent University group set up to review these situations.

**For more information,
call (423) 439-7313
or email hydea@etsu.edu**

Detach along perforation and return

***We are seeking such approval
and would like your opinion.***

1. Would you be in favor of a study such as this being conducted in this community, specifically, a study in which severely injured and bleeding patients would be enrolled without giving their informed consent?

Yes No

2. If you were severely injured and bleeding and were being treated by the paramedics in your community, would you want to be enrolled in this type of study?

Yes No

3. If a family member of yours were severely injured and bleeding and were to be treated by the paramedics, would you want him or her to be enrolled in this type of study?

Yes No

Do you have any comments or concerns you wish to share with us?

Zip code: _____ Age: _____

Gender: Male Female

Ethnic background: _____

Community Consultation and Public Disclosure Postcard Feedback

Attached are the results of the Opinion Cards returned from our postcards February 2005.

This includes 64 responses from 500 cards handed out or 12.8%

The 64 responses breakdown:

89% Caucasian

11% Did not report ethnic background

20 Male

43 Female

51 average age with youngest 22 and oldest 83

92% stated they would support the PolyHeme Study with regards to exclusion from informed consent

97% stated they would want to be enrolled in the study if they were severely injured or bleeding

95% stated they would want their family member to be enrolled in the study if they were injured or severely bleeding

Attached are copies of postcards with comments.

We are seeking such approval and would like your opinion.

1. Would you be in favor of a study such as this being conducted in this community, specifically, a study in which severely injured and bleeding patients would be enrolled without giving their informed consent?

Yes No

2. If you were severely injured and bleeding and were being treated by the paramedics in your community, would you want to be enrolled in this type of study?

Yes No

3. If a family member of yours were severely injured and bleeding and were to be treated by the paramedics, would you want him or her to be enrolled in this type of study?

Yes No

Do you have any comments or concerns you wish to share with us?

How does treatment effect
patients w/ Diabetes, on cum
adin, heart disease

Zip code: 37659 Age: 50

Gender: Male Female

Ethnic background: _____

Detach along perforation and return

We are seeking such approval and would like your opinion.

1. Would you be in favor of a study such as this being conducted in this community, specifically, a study in which severely injured and bleeding patients would be enrolled without giving their informed consent?

Yes No

2. If you were severely injured and bleeding and were being treated by the paramedics in your community, would you want to be enrolled in this type of study?

Yes No

3. If a family member of yours were severely injured and bleeding and were to be treated by the paramedics, would you want him or her to be enrolled in this type of study?

Yes No

Do you have any comments or concerns you wish to share with us?

do you try this
on animals
before you try it on
humans?

Zip code: _____ Age: _____

Gender: Male Female

Ethnic background: _____

Detach along perforation and return

We are seeking such approval and would like your opinion.

1. Would you be in favor of a study such as this being conducted in this community, specifically, a study in which severely injured and bleeding patients would be enrolled without giving their informed consent?

Yes No

2. If you were severely injured and bleeding and were being treated by the paramedics in your community,

3. If a family member of yours were severely injured and bleeding and were to be treated by the paramedics, would you want him or her to be enrolled in this type of study?

Yes No

Do you have any comments or concerns you wish to share with us?

More info. needed

We are seeking such approval and would like your opinion.

1. Would you be in favor of a study such as this being conducted in this community, specifically, a study in which severely injured and bleeding patients would be enrolled without giving their informed consent?

59 Yes No 5

2. If you were severely injured and bleeding and were being treated by the paramedics in your community, would you want to be enrolled in this type of study?

62 Yes No 2

3. If a family member of yours were severely injured and bleeding and were to be treated by the paramedics, would you want him or her to be enrolled in this type of study?

60 Yes No 3

Do you have any comments or concerns you wish to share with us?

Copies of cards with
comments attached.

Zip code: 374 -- Age: 51 avg.

Gender: Male Female

Ethnic background: 57 Caucasian

7 did not answer.

62 total response

Age range 22 to 83