Waivers of Informed Consent for Emergency Research: What Can We Learn from the PolyHeme® Experience?
John R. Mills, M.D., J.D.
Legal Counsel
Mayo Clinic

September 19, 2006
Introduction/Goals

• Discuss the PolyHeme® study, including the Legal/Compliance/IRB issues related to waiver of informed consent, and the public debate about the study.

• Discuss how the lessons may apply to future studies requesting waiver of informed consent, or more broadly to other research issues.
The PolyHeme® Study

- Multi-center study of hemoglobin-based oxygen-carrying red blood cell substitute for 720 severely injured trauma victims.

- Control arm - saline in the field, and blood in the hospital.

- Treatment arm - PolyHeme® in the ambulance and hospital, to a maximum of six units or twelve
The PolyHeme® Study

• Approved by FDA in 2003 with a waiver of informed consent in accordance with 21 C.F.R. 50.24.
• Approved during 2003 and 2004 by 31 IRBs at various trauma centers in accordance with 21 C.F.R. 50.24. One IRB disagreed, and did not approve the study.
The PolyHeme® Study

- Study progressed during 2003-2006, enrolling approximately 600 subjects.
- Independent Data Safety Monitoring Board reviewed study data and recommended continuation of trial.
- Widely publicized controversy during early 2006.
The PolyHeme® Study

  - Raises concerns about failure to disclose results of previous study using PolyHeme®.
  - 10 heart attacks (2 fatal) in PolyHeme® group, none in control group.
The PolyHeme® Study


  • “[A] clinical trial...which makes every citizen...a potential “guinea pig,” without providing a practical, informative warning to the public.”

  • “The idea that the FDA would put the burden on the public to opt out...is outrageous.”
The PolyHeme® Study

  - Acknowledged support of the concept of waived consent trials, but disagreed with IRBs’ interpretation of regulations in this case.
The PolyHeme® Study

  - Cites March 13 Grassley letter to DHHS, stating that OHRP considers the study to be “unethical.”
The PolyHeme® Study

- Hilary Williams: “God and PolyHeme basically saved my life.”
The PolyHeme® Study

  - IRB Chair describing approval of the study by her IRB. “Thoughtful, caring individuals have a right to disagree.”
The PolyHeme® Study

- It appears that a small number of institutions discontinued the study in early 2006, but the majority continued.

The PolyHeme® Study

• So do the 31 institutions where the PolyHeme® study was approved have a compliance issue?

• An ethical issue?

• A legal issue?
Other Waived Consent Studies?


  “The National Institutes of Health has set aside $5 million to study both cardiac arrest and trauma over the next five years in trials using the waived-consent rule.”
Other Waived Consent Studies?

  - Proposed use of Hemopure® on 900 trauma victims under a waiver of informed consent.
  - Previously disapproved by FDA, but apparently to be reconsidered.
So Why Do We Need Waivers Anyway?

• Generally, the investigator must obtain the informed consent of the participant, or the participant’s legally authorized representative.
  • OHRP: 45 C.F.R. 46.116
  • FDA: 21 C.F.R. 50.20
So Why Do We Need Waivers Anyway?

- Must provide information in “language understandable to the subject” and provide “sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.”
Waivers of Informed Consent

- FDA regulations (21 C.F.R. 50.24) provide an exception to allow clinical trials in cases where informed consent is deemed not feasible.

- No OHRP regulations, but the Secretary of DHHS adopted an identical exception in a “Dear Colleague” letter dated October 31, 1996.
Requirements for Waiver of Informed Consent

- 1 - Must be a life-threatening situation where available treatments are “unproven or unsatisfactory,” and ... [the study] is necessary to determine safety and effectiveness.

- 2 - Obtaining informed consent is not feasible.
Requirements for Waiver of Informed Consent

• 3 - The research has a prospect of direct benefit.

• 4 - The study could not practically be carried out without the waiver.

• 5 - The investigator attempts to contact a legally authorized representative and, if feasible, to obtain informed consent.
Requirements for Waiver of Informed Consent

- 6 - The IRB has approved informed consent document and procedures, which must be used when obtaining informed consent is “feasible.”

- 7 - IRB and/or investigator must “consult” with representatives of the communities in which the research will be conducted.
Requirements for Waiver of Informed Consent

- 8 - Public disclosure of research plans to the communities in which the research will be performed.

- 9 - Public disclosure after study to apprise community of results and demographics of the research population.
Requirements for Waiver of Informed Consent

10 - Establishment of an independent data monitoring committee to exercise oversight of the research.

11 - If it isn’t feasible to obtain informed consent, must attempt to contact the subject’s family members within the therapeutic window and ask if they object to the subject’s participation.
Main Issues Raised With PolyHeme® Study

• Are existing treatments “unproven or unsatisfactory?”
  • Kipnis et al. agreed that saline is “unsatisfactory”: “[S]aline is of limited efficacy and any promising intervention that might correct hemorrhagic shock prior to admission would appear to be worth a shot....”
Main Issues Raised With PolyHeme® Study

- Are existing treatments “unproven or unsatisfactory?”
  - Kipnis et al. objected, however, to using PolyHeme® once blood is available: “Blood transfusion has a good, if imperfect, record [in the treatment of] hemorrhagic shock.”
- Concern about “slippery slope?”
Main Issues Raised With PolyHeme® Study

- Are existing treatments “unproven or unsatisfactory?”
  - Dougherty: “Despite its widespread use and acceptance, the performance of banked blood has never been subjected to the level of scrutiny imposed on investigational drugs.”
Main Issues Raised With PolyHeme® Study

- Are existing treatments “unproven or unsatisfactory?”
  - Dougherty: Notes studies documenting side effects, and concludes “[m]any thoughtful clinicians feel treatment that increases mortality and organ failure is unsatisfactory.”
Main Issues Raised With PolyHeme® Study

• Legal/Compliance/IRB issues:
  • What level of data is required for treatment to be “proven?”
  • Does “good, if imperfect” qualify as “satisfactory” treatment?
  • How do side effects impact whether treatment is “satisfactory?”
Main Issues Raised With PolyHeme® Study

- Legal/Compliance/IRB lessons:
  - Watch for vague, undefined terms ("unproven" or "unsatisfactory") in regulations or guidance.
  - If they exist, document why IRB reached its conclusion ("The IRB determined that existing treatments are unsatisfactory because....").
Main Issues Raised With PolyHeme® Study

- What is adequate “consultation” with and “disclosure” to the community?
  - Sen. Grassley contended that consultation “emphasized the ambulance phase and de-emphasized the in-hospital phase of the... study.”
Main Issues Raised With PolyHeme® Study

- What is adequate “consultation” with and “disclosure” to the community?
- Dispute over whether deaths in PolyHeme® arm of prior study should have been disclosed. Sponsor contends they were not related to study treatment.
Main Issues Raised With PolyHeme® Study

• What is adequate “consultation” with and “disclosure” to the community?
  • Concerns about community notification and opt-out process.
  • Grassley letter cites “sparsely attended” meetings in Oregon and public meetings in Chicago with 0-5 attendees, and calls opt-out process “outrageous.”
Main Issues Raised With PolyHeme® Study

- Legal/Compliance/IRB issues:
  - What kind of due diligence is required to ensure that information provided by sponsor and presented by investigator is complete and accurate?
  - Same standard as in consent forms?
Main Issues Raised With PolyHeme® Study

- Legal/Compliance/IRB issues:
  - Can we ensure that community is properly “consulted?”
  - Many IRBs required TV, radio, and newspaper messages, plus in-person “town hall” meetings. (Dougherty: 50 newspapers, 16 radio stations, internet postings, 12 community hearings, 2 radio call-in shows).
Main Issues Raised With PolyHeme® Study

• Legal/Compliance/IRB issues:
  • How much community exposure is required?
  • Should different demographic groups be handled separately?
  • Is there a feasible opt-out process other than bracelets? Can whole groups (e.g., Jehovah’s Witnesses) opt out?
Main Issues Raised With PolyHeme® Study

- Legal/Compliance/IRB lessons:
  - Watch for vague concepts or requirements (community “consultation” or “disclosure”) in regulations or guidance.
  - If they exist, document efforts taken to meet the unstated standard.
Summary

- When standards set forth in regulations or guidance are vague or undefined, “reasonable” minds may reach different conclusions.
- When determining whether such standards have been met, document reasoning, process, conclusions as thoroughly as possible.