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An Open Letter to IRBs Considering Northfield Laboratories' PolyHeme Trial

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10 At this writing, a widely publicized waived consent trial is underway. Sponsored by Northfield Laboratories, it is intended to evaluate the emergency use of PolyHeme, an oxygen-carrying resuscitative fluid that might prevent deaths from uncontrolled bleeding. The protocol allows patients in hemorrhagic shock to be randomized between PolyHeme and saline in the field and, still without consent, between PolyHeme and blood after arrival at an emergency department. The Federal regulations that govern the waiver of consent restrict its applicability to circumstances where proven, satisfactory treatments are unavailable. Blood—the standard treatment for hemorrhagic shock—is not available in ambulances but is in hospitals. The authors argue that the in-hospital stage of the study fails to meet ethical and regulatory standards.

15 *Some months ago we prepared what was essentially the letter below. Our purpose was to alert Institutional Review Boards (IRBs) to a serious ethical/regulatory error in a widely-publicized waived-consent trial sponsored by Northfield Laboratories. The product is PolyHeme, an oxygen-carrying resuscitative fluid that might prevent deaths from uncontrolled bleeding in the field. The error was the linking of an in-hospital comparison of PolyHeme and blood (which should require informed consent) with a field comparison of PolyHeme and saline, both under the emergency waiver of consent. Although the error had been caught by several IRBs, we were not able to confirm that it had been formally reported to the Food and Drug Administration (FDA) nor that other IRBs considering or approving the protocol had been alerted. Our efforts to obtain a timely list of IRB contacts did not bear fruit. Indeed, we have written a second article (Kipnis et al. 2006) setting out in some detail the barriers we uncovered in trying to correct the error characterized in the letter below.*

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35 The three of us—Kenneth Kipnis, Nancy M.P. King and Robert M. Nelson—have been doing research on the ethics of waived-consent trials that are now permitted under 21 CFR 50.24. We have been looking at the most widely publicized example to date: the Northfield PolyHeme study.

40 It has become evident to us that: 1) there is a serious ethical flaw in this complicated and novel

study; and 2) the substance and significance of this criticism may not be reaching those who are now conducting and overseeing the research. We have learned that some IRBs have withheld approval for the reason we highlight below. All three of us have struggled with the question of what our responsibilities are when we conclude that ethically-flawed research is underway. This letter is an effort to reach the IRBs that have approved or are considering the trial.

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60 Unlike some critics, we support the concept of waived consent trials and have contributed to the effort to improve their design and implementation. We also appreciate the dangers and limitations of blood and endorse the effort to find safer and easier-to-use alternatives. However, the commercial development of hemoglobin-based oxygen carriers has been marred by a series of visible embarrassments and there is no need for another. Our goal is not to stop the PolyHeme study but to remove a defect that needlessly threatens its promise.

65 We communicated our reservations to Dr. Steven A. Gould, the CEO of Northfield Laboratories. He did not agree with us. We then posted a query to the IRB Discussion Forum (<http://www.irbforum.org/discussion/>) where, in contrast, all four respondents (including two

off-list) concurred with our critique. No responses were received from IRBs that had approved the trial. Having taken those first steps, we felt the time had come to notify the FDA, Office for Human Research Protections (OHRP) and the IRBs that have approved the trial. For a variety of reasons, no resolution emerged from that effort.

The two sections that follow are intended solely to set out background. Though some concerns are briefly discussed, they are not intended as criticisms. In the third section we set out what we take to be the core objection to the Northfield trial.

BACKGROUND: THE BASIC STUDY DESIGN

The Northfield protocol provides that trial subjects—trauma patients in hemorrhagic shock who are being treated by emergency medical technicians (EMTs)—randomly receive either saline solution or PolyHeme. Enrollment occurs in the field under the waived-consent exception and before arrival at an emergency department. The waiver is properly applicable because, first, persons in hemorrhagic shock are at risk of dying unless treated promptly. Second, apart from slowing blood loss, replacing fluids and getting the patient to an emergency department, hemorrhagic shock is not treatable in the field. Finally, consent is not likely to be possible within the therapeutic window. In particular, the prospective research subject is unlikely to be capable of consent, either because of injuries or because of the gravity of the situation and the complexity of the consent process. Nor is a legally authorized representative likely to be available.

Once at the hospital, efforts will be made to secure consent for continued participation either from the patient/subject or from a legally authorized representative. However, if formal withdrawal from the study does not occur, participation continues by default in the hospital even if consent is not obtained. Patients/subjects in the control group receive standard treatment: saline and blood as needed. However, patients/subjects in the experimental group continue to receive PolyHeme instead of blood for oxygen delivery: up to six units of PolyHeme for up to twelve hours, at which point their participation in the trial ends. The study thus can be divided into two phases. The first (PolyHeme vs. saline) occurs in the field. The second phase (PolyHeme vs. blood) occurs for up to twelve hours after hospital admission.

We had wondered about the practical reason for the 12-hour clinical phase. Emergency departments like those participating in the Northfield study typ-

ically receive trauma patients less than one hour post-injury. But the trial mimics a 12-hour period without access to typed and cross-matched blood. Unlike remote areas and ships (which do not appear to be participating in this study), we expect that 12-hour field evacuation delays are either uncommon or unheard of in the communities where the studies will be conducted. Why include this troubling feature so early in a research program?

The delay reflects the circumstances of combat-wounded soldiers when evacuation to field hospitals is impossible and a safe and effective oxygen-carrying resuscitative fluid could save lives. If these well-known military constraints help to explain the design of the clinical phase, then any additional risks that might be imposed upon hospitalized civilian trauma victims would benefit neither the patients/subjects nor those subsequently injured in their communities but, rather, soldiers fighting overseas: a different population. While all of us endorse the obligation to provide the highest-quality care to injured American troops (and to others at a distance from blood banks), we think such a duty cannot justify a possible departure from ethical principles governing research on non-consenting civilian human subjects. But does the research design involve such a departure?

MORE BACKGROUND: POLYHEME VS. BLOOD

The scientific argument for the second phase of the study places great weight on the well-known immunological problems with allogeneic blood and the suspicion that these are responsible for multiple organ failure and death. PolyHeme appears not to have that disadvantage and there is a reasonable hope that its availability would improve outcomes following hemorrhagic shock secondary to trauma. Taken together, these are good reasons for evaluating the safety and efficacy of PolyHeme in head-to-head comparisons with blood. Definitive research has not been reported and the proposed clinical studies may answer some questions.

Here are two outstanding empirical issues. There is a question whether the greater incidence of multiple organ failure in transfused trauma patients is due to the severity of the initial injuries or to the transfusions afterwards. The evidence of correlation suggests, but does not establish, causation: While the number of bandages used on a trauma patient could correlate with the probability of death, no one would conjecture that bandages cause death. Second, the absence of clotting factors in PolyHeme raises a question whether bleeding

175 secondary to trauma will be adequately controlled
in hospitalized patients who receive it instead of
blood. PolyHeme could cause deaths in this way
(and possibly in other unknown ways).

180 We were advised that the protocol allows the use
of coagulation products in the event that bleeding
is a continuing problem during the 12-hour/six-
unit clinical phase. Obviously there would be eth-
ical concerns if these common treatments were to
be withheld (along with blood), and patients could
suffer or die as a consequence. But the clinical use of
coagulation products raises a different concern. For
185 if these products are routinely administered during
the clinical phase of the trial (as needed to control
bleeding), and are not available in the field, then the
12-hour post-admission phase of the trial would fail
to mimic extended field evacuation times in either
civilian or military settings. In particular, improved
survival rates could not show that PolyHeme can be
safely and effectively used in settings where those
coagulation products were not also available (i.e., in
the field).

195 Even so, it seems that PolyHeme's incompletely
understood disadvantages (decreased coagulation
and perhaps other unknown adverse effects) and
allogeneic blood's better understood shortcomings
(increased risk of inflammatory response, etc.) make
200 it impossible to judge now which of the two is in-
ferior in the treatment of hemorrhagic shock sec-
ondary to trauma. In that respect, clinical research
may be in order. We will assume in what follows that
the science behind the study is sound and that the
time has come for head-to-head randomized com-
parisons of PolyHeme and blood. But after consid-
erable correspondence and reflection, we have come
205 to believe that the design of the Northfield protocol
is nevertheless seriously flawed.

210 **THE CORE OBJECTION TO THE NORTHFIELD
TRIAL**

Saline cannot correct hemorrhagic shock and, in
consequence, patients with traumatic injuries often
die of blood loss before reaching the hospital. For
215 waived-consent trials, the patients/subjects must be
in life threatening conditions and proven, satisfac-
tory treatments must be unavailable. As the FDA
has put it in its Guidance, the patients/subjects
must be suffering from "diseases or conditions where
220 the likelihood of death is high unless the course of
the disease or condition is interrupted" (FDA 2005).

Blood transfusion has a good, if imperfect,
record as the favored method of interrupting the

natural course of hemorrhagic shock. Accordingly,
the waived consent field trial of PolyHeme is jus-
225 tifiable just because blood is not available in the
field. But blood is available in the hospital, and
that salient fact rules out any head-to-head com-
parison of PolyHeme and blood under the waived-
consent regulation. Like all medical interventions,
230 blood has its risks and limitations, and, as suggested
earlier, clinical trials should be comparing it with
experimental interventions—like PolyHeme—that
might be more satisfactory in some ways, but only
with proper consent. 235

On one side are the standards that underlie the
informed consent exception in 21 CFR 50.24 and its
approach to the narrow category of waived consent
trials, where no satisfactory treatment is available.
On the other side are the more familiar baseline stan-
240 dards that enter into the design of ordinary clinical
trials, where a possibly safer and more effective ex-
perimental treatment may be available. These must
be sharply and carefully distinguished, bearing in
mind the equivocation in the term "unsatisfactory."
245 Saline is plainly an "unsatisfactory" treatment for
hemorrhagic shock, but not in the same sense that
blood might be. In the field, blood—the only ap-
proved and effective treatment—is unavailable, pre-
ventable deaths are common, and all EMTs can offer
250 for hemorrhagic shock is a high-speed trip to a hos-
pital. Under the circumstances, saline is of limited
efficacy and any promising intervention that might
correct hemorrhagic shock prior to admission would
appear to be worth a shot, even if consent were
255 not obtainable. In contrast, blood transfusion—the
standard treatment for hemorrhagic shock—is read-
ily available in the hospital-based clinical phase of
the trial, as well as an unproven (possibly better)
experimental treatment that can be approved for
260 testing, but only on consenting patients. The amal-
gamation of two very different types of trial (Poly-
Heme vs. saline and PolyHeme vs. blood) under a
single consent standard has erroneously conflated
two quite different regulatory approaches. 265

To avoid misunderstanding, we wish to re-
emphasize that we are not challenging the scientific
soundness of the in-house phase of the trial. We
can accept the legitimacy of a head-to-head ran-
270 domized clinical trial comparing blood and Poly-
Heme, but only with consenting patients/subjects.
We don't need to be reminded of the risks associated
with blood. It is enough that no one knows whether
PolyHeme or blood offers a better chance to patients
275 in hemorrhagic shock secondary to trauma. That is
why a clinical trial is warranted.

280 What we are challenging is the extension of
the 50.24 exception to an active controlled study.
The regulations that create the waiver anticipate
patients/subjects for whom there are only unsatis-
285 factory options. It is therefore a mistake to stretch
the regulations to include patients/subjects with op-
tions that fall short of perfect safety and efficacy. Too
few patients will be left out if the phrase “unsatis-
290 factory treatment” is given such a liberal interpre-
tation. Accordingly, the waiver should cease to ap-
ply as soon as suitable blood is at hand. Thereafter,
consent to an in-house, active-controlled trial—
and not merely a good faith effort to obtain it—
295 is plainly required before clinicians can forego the
standard treatment, routine transfusion, and in-
stead randomly substitute a promising experimen-
tal alternative. Studies like this one ought to move
forward, but never under 50.24’s waived consent
exception.

300 Consider that it is inevitable that hospitalized
patients/research subjects on PolyHeme will die, if
only because of the severity of their initial injuries.
When deaths occur during the critical 12-hour in-
terval when available blood is medically indicated
but being withheld, plaintiffs’ attorneys may want
to scrutinize the records carefully to ground claims
of liability. Putting the point most dramatically,
305 these men and women will have died while being
denied an available treatment (blood transfusions)
that is indicated by the standard of practice, follow-
ing unconsented-to enrollment in a research study.
Despite encouraging results in earlier trials, the use
of PolyHeme is still an investigational procedure
310 that can only be substituted for established prac-
tices with consent (except under circumstances that
do not obtain in the hospital setting). Litigation
flowing from this mistake would likely do damage
to Northfield, to the hospitals and universities that

are running what we believe to be an ethically flawed
study, to the credibility of the FDA and its imple- 315
mentation of the 50.24 rule, to medical research
in general, and to the hope of having a near-term
alternative to blood.

320 At a minimum, we believe it is obligatory to
separate the field trial and the hospital-based clinical
trial. We think it is a serious and ongoing error to
be piggy-backing the latter onto the former, with
its waiver of consent—a narrow exception drafted
for significantly different circumstances. We are in
agreement with those IRBs that have thought it 325
a mistake to enroll non-consenting subjects into
a post-admission study comparing PolyHeme and
blood. We believe that, once this flaw is pointed out,
IRBs should revisit their earlier decisions to approve
the study and— if the study is still underway— 330
clinicians should cease administering PolyHeme to
non-consenting patients/subjects as soon as cross-
matched blood can be made available. Of course, if
we are mistaken about the flaw in the Northfield
study, we would like to learn of our error. 335

In the future, open letters like this one may en-
courage collaborative multi-site communication on
questionable research, thereby increasing the like-
lihood of correction when protocols are seriously
defective. ■ 340

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