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AND UNITED STATES ARMY

WORKSHOP ON CRITERIA FOR SAFETY AND EFFICACY EVALUATION OF OXYGEN THERAPEUTICS AS RED CELL SUBSTITUTES

MONDAY,

SEPTEMBER 27, 1999

The Workshop took place in the Natcher Conference Center, NIH, Rockville, Maryland at 8:00 a.m., Jay S. Epstein, M.D., Chair, presiding.

PRESENT:

JAY S. EPSTEIN, M.D.	Chair
ABDU I. ALAYASH, Ph.D.	Speaker
LOU CARMICHAEL, M.D.	Speaker
STEVE A. GOULD, M.D.	Speaker
WILLIAM D. HOFFMAN, M.D.	Speaker
PETER E. KEIPERT, Ph.D.	Speaker
HARVEY KLEIN, M.D.	Speaker
MICHAEL E. SAUNDERS, M.D.	Speaker
TOBY SILVERMAN, M.D.	Speaker
BARBARA ALVING, M.D.	Panel Chair
PAUL AEBERSOLD, Ph.D.	Panel Chair
JEFFREY L. LARSON, M.D.	Panel Member
STEPHEN M. COHN, M.D.	Panel Member
JAMES J. HOLCROFT, M.D.	Panel Member
MICHAEL J. JOYNER, M.D.	Panel Member

PRESENT (Cont'd):

MARGOT S. KRUSKALL, M.D.	Panel Member
PAUL M. NESS, M.D.	Panel Member
REUVEN RABINOVICI, M.D.	Panel Member
RICHARD B. WEISKOPF, M.D.	Panel Member
GUS J. VLAHAKES, M.D.	Panel Member

ALSO PRESENT:

ED SLOAN

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

8:03 a.m.

DR. ALAYASH: Okay, good morning and welcome to the FDA-sponsored workshop on the safety and efficacy evaluation of red cell substitutes. My name is Abdu Alayash. I am with the Center for Biologics Evaluation and Research. This workshop is also sponsored by the National Institutes of Health and the United States Army.

Just to spend a couple of minutes to acknowledge the people who actually helped us in putting the program together. On your left, the names of the individuals, part of the steering organizing committee, who helped us in putting the program together. On the other side, the names of the panel members who were willing to come and take part in this workshop. Of course, we are very grateful to that. The affiliation and specialties are listed in your packet.

A couple of housekeeping announcements. We, unfortunately, do not have any microphones on this side. We were planning to have two on both sides in either of these rooms. So one suggestion, if you don't mind, is to fill a question on the piece of paper which is in your package and pass it on to Beth and Felice, who will be on both sides of the

aisle. And then they will pass the question either to the panelist or to the speaker at the time.

Also, I have been told that food and refreshment are not supposed to be here in this room. Speaking of food, the cafeteria is on the left as you leave this hall. I think that is about it. Let me now introduce Dr. Jay Epstein. Dr. Epstein is the Director of the Office of Blood Research and Review.

DR. EPSTEIN: Thank you very much, Abdu. Good morning and welcome to everyone. I have actually never seen this room set up this way with a tandem theater. I hope you can all see the speaker. I think that it is noteworthy that this is a co-sponsored meeting, which is being hosted by the FDA, the NIH, and also the U.S. Army. From an historical point of view, FDA has been involved with the issue of reviewing blood substitutes since the mid-1970's, with the initial development of a hemoglobin product by Warner Lambert. The administration of unmodified and partially purified hemoglobin products cause severe renal damage, which at that time was an unexpected finding. And the experience with the early hemoglobin-based oxygen carriers has shown that there can be toxicity to many organs and systems from an unmodified or even from a modified hemoglobin-based product. Similarly, the early research with

perfluorocarbon-based emulsions demonstrated a number of adverse events in preclinical trials and also clinical trials.

The field of oxygen therapeutics then sort of went into a lull with some discouragement, but then a resurgence of interest in the mid-1980's, after the emergence of HIV and the tragedy of blood transmission and then the increasing concern about other blood-borne pathogens, particularly hepatitis agents. Even though the screening and detection methods for the currently known transmissible agents now have resulted in a very safe blood supply, as will be reviewed by Dr. Klein, there is still the Holy Grail of products which can be infection free, and this has sustained interest in blood substitutes.

In spite of the biotechnological advances of recent years in understanding the basis of the toxicity of hemoglobin-based oxygen carriers and perfluorocarbon-based emulsions, there are still unsolved problems. In 1989, FDA established its own research program in this area led by Abdu Alayash, and I just would like to take a moment to recognize Abdu as the lead chairperson for this workshop and also to acknowledge his scientific success, particularly in helping elaborate the role of nitric oxide in vascular relaxation. We all know Abdu as a

hemoglobin expert.

The issues of safety of oxygen therapeutics have been addressed twice before by FDA, once in 1990 and again in 1994, with the help of many outside experts, many of whom are again here today. CBER was able to issue guidance, first in 1990 on safety and then in 1994 on efficacy criteria for evaluation of hemoglobin-based and perflur chemical-based oxygen therapeutics.

Much has been learned in the last 10 years about the biology, physiology and pharmacology of various types of oxygen therapeutics, but much more remains to be elucidated. We know more about the toxicities of adverse events associated with these complex products, and we know that there is still room for progress.

Demonstrating the efficacy of oxygen therapeutics remains itself a significant challenge. Doing so with an acceptable safety profile will be difficult given that the comparator products are safe blood products. Over the next day-and-a-half, we will be addressing a number of questions related to the assessment of clinical efficacy and safety in different settings, such as elective surgery and trauma. FDA is most interested in what the blood substitute community has to say in regard to these

important issues, since you will need to live with the standards that we establish.

We recognize that the development of a new class of products presents many challenges -- scientific, economic, et cetera. It is our hope that through workshops of this sort, we will be able to develop a set of guideposts toward the eventual approval of safe and effective hemoglobin-based products for appropriate indications.

At this point, it is my pleasure to turn the program over to Dr. Harvey Klein, who is the first speaker in Session I, well known as the Director of Department of Transfusion Medicine at the NIH Clinical Center and a well-known leader in the field of blood therapeutics.

DR. KLEIN: Thank you, Jay. It is a pleasure to be here. I have been an advocate of alternatives that carry oxygen since the mid-1970's. The reason for that primarily is the toxicity of blood components during the early and mid-1970's. Today, as you all know, the situation is just a bit different. During the next 20 minutes or so, I would like to show you where I think we have come in the past several years. I would also like to point out that availability is also a safety issue. And as we have increasingly made the blood supply

safer by eliminating risky donors and donors who aren't so risky, we have begun to compromise the ability to provide safe blood to patients in the United States.

There are a variety of different risks in 1999. I will concentrate primarily on the transmission of infection, but in fact hemolytic transfusion reactions are still a fatal complication of blood transfusion and the risk has not declined dramatically over the last years as the transmission of infection risk has.

Alloimmunization with red cells still occurs about 1 percent per unit transfused. We have fatal pulmonary reactions, which are primarily a result of plasma infusions, but also of plasma and white cells contained in our red cell transfusions. Allergic reactions are still fairly common but relatively mild. Anaphylaxis occurs in about one in a million transfusions. And then there is the issue of immunosuppression.

Just to start with fatal acute hemolytic transfusion reactions, although there hasn't been much advance in the past several years, this is really quite a success story. If you go back to the 1940's when Kilduffe and DeBakey reported their series, about one in a thousand units of blood

transfused resulted in a fatal hemolytic transfusion reaction, and these were primarily because one didn't adequately identify the donor and the recipient. Lest you think that was an outlier, these same data were available in 1943 from a separate source. You can see, however, that over the years as the ability to identify donor and recipient improved, the rate of fatal hemolytic transfusion reaction declined dramatically. Today it is about one in half a million units transfused or about the same as the risk of HIV in transfusion. So it is still there, but it is dramatically better than it was much earlier.

These are data from Jean Linden, which were published in the early 1990's trying to emphasize this point. She looked at data in New York State and she found that erroneous transfusions -- giving the wrong blood to the wrong patient -- were actually reported about once in every 19,000 transfusions. ABO compatibles about once in every 3,000 transfusions, and that resulted in a fatality of about one in every 600,000 transfusions. Then by mathematical correction for underreporting, they looked at the rate of giving the wrong blood to the wrong patient. They came up with a number which is fairly compatible with what has been found earlier;

that is, one in ever 12,000 units is given to the wrong patient, a number I still find an astonishing figure. So we have quite a ways to go.

Now when one looks at transfusion of infectious material, there are several conditions that are necessary to be met. First of all, there must be an asymptomatic viremic phase in the blood donor. The virus must be viable in the storage conditions, usually 4 degrees Centigrade for red cells. There must be a sero-negative or better said a susceptible recipient population. Lots of viruses are transmitted by blood, but in many cases the recipients are not susceptible to these viruses. And finally, the agent must be capable of inducing disease. And as we are finding increasingly, viruses that are transmitted by blood don't necessarily transmit disease, at least not disease that we can identify.

A good example is hepatitis A, a small non-enveloped virus, where we don't really see transfusion transmitted disease in single units of red cells. Why is that? The primary reason is that there really is no carrier state of hepatitis A. So that if a donor is infected with hepatitis A, that donor frequently becomes ill very quickly, has a time-limited illness and recovers entirely. So you

would have to be quite unlucky to catch that particular donor in the period where he or she is infected with hepatitis A but is not yet ill. These cases are so uncommon that with individual units of blood, they are almost reportable.

Hepatitis B is a different situation. While the red antigen was discovered back in 1962 and testing has been available since 1968, we now have extremely sensitive and specific tests for the hepatitis B surface antigen. And as you know, all blood in the United States is screened and has been screened for many years. We also have other serologic tests to close the sero-negative window. And finally, there is a hepatitis B vaccination, which is now recommended for all children and certainly has been recommended for all health workers for many, many years. This is still a risk. I will give you some numbers on that in just a moment. But clearly a much lower risk than it was several years ago.

For those few of you, if there are any, who don't know what the serologic window is, if one is infected with a virus at time zero, there is a finite period of time before a). either signs develop such as jaundice or symptoms or elevations of liver function tests or serologic evidence that the virus

is present in the infected individual. And whether that is the viral antigen or an antibody or several antibodies made by the individual, this period, the serologic window is the period during which a donor may donate blood which may be infection, although the donor appears to be entirely normal by both history and physical examination and serologic testing.

If one looks at the serologic windows for some of the common agents -- here they are. Using anti-HIV and p24 antigen for HIV, we have an estimated serologic window of about 16 days, with as you can see a substantial range. For HTLV, about 51 days with a range of 36 to 72. And strikingly for hepatitis C virus, an estimated serologic window of 64 days with a range going all the way up to over 100 days. This is hepatitis B, an estimate of about 56 days.

Hepatitis C remains a major problem in blood transfusion. 200,000 new infections occur annually in the United States. However, less than 5 percent of those are related to transfusion. Clinical illness occurs between 2 and 26 weeks after the individual is exposed, and the signs and symptoms are usually minimal. So we do rely heavily on our screening tests. Fulminant hepatitis with the C agent is so unusual as to be almost reportable.

Why are we worried about hepatitis C as a transfusion transmissible agent? Well, 85 percent of those who develop hepatitis C infection develop a persistent infection. New evidence does indicate that about 15 percent of people either totally clear of the virus or have an infection that does not progress. However, 20 percent of individuals infected go on to develop cirrhosis, even though this may take 18 or 20 years. Physical signs and symptoms are mild and they fail to predict the severity of the illness, and this is an infection associated with hepatocellular carcinoma.

Just to give you some data, these are actual numbers from the National Institutes of Health, where we had an open heart surgery program for many years and followed patients transfused with red cells prospectively. When I arrived at NIH back in the early 1970's, as you can see if you had open-heart surgery, you had about a one in three chance of leaving the hospital with post-transfusion hepatitis. Because in the early 1970's, we went to an all-volunteer blood program and introduced hepatitis B surface antigen testing and reduced the number of units per case of open heart surgery, you can see a dramatic drop in overall post-transfusion hepatitis. There is a drop in hepatitis B obviously with the B

screening, but the overall drop in hepatitis is most dramatic.

Other things that were subsequently introduced to reduce the risk did in fact prove effective. Increased sensitive and specific hepatitis B surface antigen screening tests, screening with ALT, removing high risk populations during the AIDS epidemic, screening with anti-COR antibody, and finally very dramatically using anti-hepatitis C virus screening has literally eliminated post-transfusion hepatitis from the populations that we have studied in the National Institutes of Health. And in Dr. Harvey Alter's studies now in the last 700 or so patients prospectively studied, not a single case of clearly associated post-transfusion hepatitis has been seen. But most Americans aren't all that worried about hepatitis, they are worried about HIV. One in 300 Americans now carry this virus, and 90 percent of those who receive an infected unit will themselves become infected. We have introduced screening questions as all of you know, and all blood in the United States is now tested not only with the antibody for HIV but also with HIV antigen. I think these numbers may be a little out of date, but certainly less than 50 cases of post-transfusion hepatitis have been reported

since 1985. Now think about that. About 11 million units of red cells transfused every year in the United States and fewer than 50 infections since 1985 have been reported. Even if that is way underestimated, double or triple the number, there is still a dramatic improvement in blood safety.

I think this is a very important slide that I would like to point out when people are thinking about safety of blood transfusion. It is a study published by Mike Busch. It shows data collected from frozen specimens in San Franciso, looking at infection with HIV in the years starting with 1978 and going through 1990. This is the risk of HIV for units transfused and the percentage. The important points here are first that the risk was extremely high in San Francisco before the first cases of AIDS were ever reported. Not transfusion-transmitted HIV, but cases of AIDS at all. It was even higher before the first hemophilia-associated AIDS case was reported. And it certainly was extremely high, maybe as high as one percent in San Francisco before the first transfusion-associated case with a unit of platelets was reported in a child in San Francisco.

Now much as the blood collectors have been criticized for slow reaction, the removal of

high risk populations by donor screening long before there was any test for HIV dramatically reduced the risk of transfusion-transmitted HIV in San Francisco. With the implementation of HIV antibody screening in March of 1985, you can see the risk virtually fell to zero.

Again, these are data just to give you an impression of what it was prior to screening and testing. 400 cases per million units in the United States. If you move through 1985 to 1987 to 1990 and 1991 to 1992, you can see the dramatic decrease in risk of HIV, with a dramatic closing of the window of serum negativity. And now with the introduction of NAT testing, nucleic acid testing, we assume that there will be one case or less with a window of about 11 days.

If all of that is a success story, why are we still worried about blood safety. The reason is that there are a lot of emerging risks of blood transfusion. Other retroviruses, a variety of parasites, prions we keep hearing about, and new viruses such as hepatitis G virus, which is probably not a hepatitis virus but a GT virus, and tick-borne illnesses and a variety of bacteria.

With apologies to Gary Larson. This is how viruses get around. "You are from France? Wow.

Say, you have lovely eyes." And the viruses say, "Hey everyone, we are going to Paris." It is a small world. And while the blood supply in the United States in 1999 appears to be extremely safe, we know that there are other agents around the world which are very likely to be imported into the United States. This is just an example in 1996 of a new retrovirus associated with AIDS and not picked up by the current screening tests, which while not in the blood supply was found in the United States. We are very likely to see more.

On a worldwide basis, of course, malaria is the most important transfusion-transmitted infection. But in fact, there have been 103 cases reported in the United States between 1958 and 1998, about four cases -- a case per 4 million units of blood transfused each year. When someone is infected with malaria, the parasitemia may persist at low levels for many, many years. We have no licensed or no effective screening test -- licensed or effective screening test. So screening by history remains the mainstay, and it is very effective. It defers 97 to 99 percent of individuals who are at risk. However, it is not 100 percent effective. History, of course, may be inaccurate, and frequently when we do see a case of post-transfusion malaria, it is because of an

inaccurate history.

We do see bacteria in blood. These are data from the American Red Cross where red cells were infected about .2 percent of the time. Here you see the rate of febrile reactions. Deaths are extremely rare, probably underreported, but they certainly do occur. We have no way of screening for bacteria in blood right now that are effective. For example, when there seemed to be an outbreak of Yersinia in the U.S. blood supply, it was very clear that screening tests were ineffective. People tried screening with histories -- history of diarrhea, since that is what is associated with the Yersinia organism. When one looks at the number of normal blood donors who may have had diarrhea or some gastrointestinal upset in the two weeks prior to donation, one could never use that as a screening criteria.

And finally, if you consider that the older the blood is, the more like you are to get extreme bacterial growth, shortening the storage of blood -- with Yersinia, shortening the storage of blood to any reasonable level would have decreased the number of units by 10 percent. Again, not a very practical method of protecting the blood supply.

There are also issues with tick-borne

illnesses. Not that long ago, a tick-borne illness outbreak in Fort Chaffee in Arkansas resulted in the military removing a large number of potential blood donors for six months from the donating population.

Creutzfeldt Jakob disease, a dementing illness with both familial and sporadic patterns of occurrence has been transmitted by brain tissue, by dura mater transplants and even in one instance by a corneal transplant. We know that about 3,000 patients were infected when they were given human growth hormone between 1983 and 1995, and that the latency of this disease is measured in years. Could it be transmitted by blood? Well, neither animal studies nor epidemiologic patterns support blood-borne transmission. Animal studies at best are inconclusive. Looking at transfusions in 202 CJD patients, they don't differ from matched controls in their transfusion exposure. No CJD patients with hereditary coagulopathy or hemoglobinopathy was found. So patients heavily transfused don't seem to develop CJD. In look-back studies in donors who subsequently turn out to be infected with CJD, they do not identify recipients of blood who have been infected. So all of the data suggest that it isn't transmitted by blood, but we are not really sure. So we do have screening questions to try and decrease

that small potential risk to the recipients of blood.

And now we have mad cow disease, the so-called variant Creutzfeldt Jakob disease. First described in 1996, it is linked to bovine spongiform encephalopathy, mad cow disease. 39 deaths were reported through March. The mean age is 29 years, so these are young people. In the last quarter of 1998, nine deaths were reported in England. Now there has been no association with blood. In fact, in every way one can look at this disease, there has been no association with blood. But we don't have enough data on this. So, in fact, we have a number of unanswered questions. Can blood transmit CJD or new variant? If so, what is the agent? Is it a prion? And if it can be transmitted, what are the circumstances? Do all blood components transmit? Does dose matter? Does the duration and number of transfusions matter? And finally, is there a rational public health intervention? The Canadians thought so, and have in fact banned blood transfusions from individuals who spend time in the United Kingdom. Recently our own FDA has in fact put some guidance out there suggesting that individuals who spend six months in the United Kingdom between a given period of time not be eligible to donate blood.

Let me close with what I think are the

estimated risks in 1999 per unit of blood transfused. Mild allergic reactions are relatively common, but more of a problem for the physician than for the patient. Hemolytic transfusion reactions still occur about once in every 6,000 transfusions but are fatal only about once in every half a million, about the same rate one finds with HIV infections. And this is likely to go down even more with the introduction of NAT screening tests. Hepatitis B infection may be somewhere in the range of 1 to 66,000, although many people feel this is an overestimate and it is less frequent than this. Hepatitis C is about 1 in 100,000. And again, going to decrease dramatically as the window is closed with NAT testing. HTLV infection, again about once in every half a million units transfused. Bacterial contamination of platelets may be as common as once in every 2,500 units, much less common in red cells. Acute lung injury seen primarily with plasma components, but still seen with some red cell and whole blood transfusion, once in every 500,000 units, and the same is true for anaphylactic shock. Graft versus host disease, and immunomodulation, we really don't know very much about.

So in summary, there are about 16 million units of cellular components transfused in the United

States every year. Our advances in blood screening and in testing and in processing have improved safety dramatically. Any blood substitute is going to have to compete with this dramatic improvement in safety of red cells. However, zero risk, while an admirable goal, is really quite unrealistic and we are not going to see that. The risk of emerging issues will always be there. And finally, in terms of such things as mad cow disease and new variant CJD, well-meaning interventions must not compromise safety. As we do decrease the availability of blood components, we increase the risk to the potential recipient. Thank you very much.

DR. ALAYASH: Could we have the first slide, please? Okay, what I am going to basically do in this 25 minutes or so is give you an overall profile of the safety of some of the current generation of red cell substitutes with some emphasis on the biochemical bases that are responsible for some of the clinical and preclinical events being reported in the literature.

You have seen this cartoon before. It helps in just basically summarizing the number of products that we deal with, both from a regulatory point of view and from a research point of view. There are basically two classes of compounds. The

fluorochemical-based products and hemoglobin-based products. For the fluorochemicals, they are basically synthetic molecules. They are primarily made of carbon proteins in which the hydrogen atoms are replaced with fluorine. These compounds are hydrophobic and of course they need to be emulsified, usually with surfactants, normally a phospholipid-based product. These compounds have high ability to solubilize a number of gases, including oxygen.

The hemoglobin-based products, of course, they are derived from the red cells, either from outdated human blood or animal outdated blood. The protein is extremely purified as a starting material. We have basically two types of starting material, either an extremely purified A zero or a stroma-free hemoglobin. Stroma-free hemoglobin means clearly the stromal components be removed. It may or may not still have some of the red cell protective enzymes such as catalase and SOD. These products, these A-zero or stroma-free hemoglobin, have been either cross-linked or cross-linked and the surface of the protein is decorated with non-protein components and/or polymerized. One of the most commonly used polymerizing agents is glutaraldehyde. The result, of course, you have a collection of protein with different sizes. In some instances, the tetramer is

either eliminated or reduced to 1 or 2 percent. Other options, of course, is to encapsulate the hemoglobin, and none of these have reached the FDA as yet. The product that we will be dealing with for today's discussion is polymerized and conjugated hemoglobin and a little bit of history on diaspirin phosphohemoglobin, which is a tetrameric hemoglobin.

The purpose of modification is basically for two reasons. It is to keep the heat tetramer intact. And second to that is of course to manipulate the oxygen affinity. Most of these reagents are bifunctional. They stabilize the protein and also they lower the oxygen affinity of the hemoglobin.

In terms of difference between the two classes of compounds, this is the typical titration curve, which shows you the difference really in terms of oxygen affinity between fluorochemicals and hemoglobin with the red cells. As you can see with fluorocarbons, they linearly depend on the oxygen tension, and that would mean, of course, if it is given to a patient, the patient has to be ventilated with 100 percent pure oxygen. In the case of hemoglobin, of course, it is typically within the red cells or outside the red cells, they exhibit that sigmoidal and cooperative interaction between the

different subunits, which also mean that hemoglobin can deal with very little oxygen and can deal with a high amount of oxygen.

The interactions of oxygen with the fluorocarbon is very weak, and that of course means that you will be able to extract more oxygen from fluorocarbons than you would actually do from red cells or from free hemoglobin.

In terms of safety of the fluorochemicals, the literature is really very limited. There is very little independent research out there as far as the safety of fluorocarbons. There are a couple of issues that keep popping up every now and then, issues such as complement activation or platelet lowering effect. The mechanism is not really well understood.

This is basically the extent of my coverage of fluorocarbons. I am going to switch back now to hemoglobin, simply because we have a lot of information available in the literature. This is a summary. If you read the literature now, this is the list of things that you will come across. This is, remember, not really a comprehensive list. It is based largely on studies done in animal models -- in a variety of animal models and a variety of sizes of animals, small and large.

The major issue here, of course, is the ability of hemoglobin to react with nitric oxide produced by the vascular system. This leads to vasoconstriction. Both systemic and pulmonary vasoconstriction has been seen in animal models. Macrophage activation leading to cytokine release. This has been reported in earlier animal models. More recently last month by Jack Levin, who also reported the macrophage activation in animal models with a pre-existing sepsis. Vasculitis -- this is an issue reported by the Dutch Army Research group using polymerized hemoglobin with glutaraldehyde. They attributed that transient lesion largely due to the polymerizing reagent rather than to the protein itself.

Platelets and red cell issues. There are a number of in-vitro experiments reported in the literature revealing interactions between hemoglobin and the red cells. There aren't really up-to-the-point recently good animal models. Again, the assumption there is that hemoglobin interferes with the platelet physiology. Barbara Alving reported a few years ago in her surgical model that hemoglobin, diaspirin cross linked hemoglobin caused disposition of platelets. More recently, Colin McKenzie has actually a couple of papers coming out very recently

in his severe hemorrhagic shock dog model, reported that PHP, polymerized cross linked hemoglobin -- excuse me, conjugated and cross linked hemoglobin caused platelet and red cell aggregation in that particular model.

Rapid oxidation to methemoglobin -- this is largely a theoretical concern up to this moment. There are, however, a couple of good studies which were done recently, and I will come to that a little bit later on.

In terms of free radical injury, again it is largely theoretical and largely done in-vitro. One early experiment was done by George Biro using stroma-free hemoglobin in titer assays of free radical injury. But of course, if we look for markers of cellular damage, we can actually see that a number of these animal models are reported in the literature. The endotoxin effect -- this is largely pioneered by Jack Levin and a couple of other laboratories, where they suggestion that the attraction between endotoxin and the hemoglobin can actually lead to activation of endotoxin. Hemoglobin can also influence the LPS clearance from separation, and in some instances the hemoglobin increased lethality. The mechanism for that is not well understood, but there are a number of animal models

to support that.

In terms of human clinical trials, of course this is very difficult to collect from the literature. But there are, however, recent reports largely from manufacturers. Again, vasoconstriction and hypertension were seen in a number of these clinical trials whether with normal volunteers or in some trauma or in some elective surgery. Again, the hypothesis here is largely because of the interference of hemoglobin with the vascular system.

GI distress varies from mild to moderate. Abdominal discomfort is again being reported with most of the proteins that have been reported in the literature.

Excessive mortality -- I specifically refer here to a study that has just recently been published using diaspirin cross linked hemoglobin. This is a study published by Baxter Research Associates in Europe in acute ischemic stroke. Of course, they reported that there is more mortality in the diaspirin cross linked hemoglobin group than in the normal individual. They did not obviously explicitly suggest that hemoglobin is a neurotoxic, but they reported the classic symptoms from high blood pressure and sustained blood pressure in the group of people that received diaspirin cross linked

hemoglobin to all sorts of hepatic and pancreatic enzyme elevation.

If you want to sort of look again at the literature and try to come up with what the community is really thinking as far as the pressor effect of hemoglobin, which seems to be the predominant thing in here, clearly the nitric oxide binding is an issue. The issue of the size of the protein will come quite frequently in the literature. Another suggestion which came from Bob Winslow and his group in San Diego is that what you see is basically an autoregulatory effect; i.e., because the products are low-oxygen affinity products, they deliver oxygen. This flux of oxygen triggers vasoconstriction as a part of autoregulatory mechanism. There aren't many sort of support in the literature from different sources, but this is an important issue that we need to consider.

Increased endothelin secretion -- again, this is pioneered by Anil Gunarti and more recently Sheila Muldoon from USUHS. They seem to suggest that endothelin, which is a natural vasoconstrictor, is actually increased. And in fact if you go back to the study that I have just mentioned, the safety study in the stroke patients, they indeed measure endothelin and they found elevation of the level of

endothelin in the serum of these patients, and so on and so forth.

These are really the main predominant mechanisms. Of course, the nitric oxide is really on top of the list simply because we have a large amount of data there based on human and animal organs which support this mechanism.

So what about nitric oxide? As you all know, the revolution of nitric oxide started almost ten years ago, and of course it affected us and the blood substitute community quite dramatically. Now we know, of course, that nitric oxide is EDRF produced by the vascular system by a very sophisticated enzymatic machinery from L-arginine. It is short-lived and reacts with oxygen and a number of molecules. If you try to list the function of nitric oxide, there is of course a huge list. These are some that are relevant to us. Most important really -- the two functions that I think are relevant to us of course is vasodilatory functions, and a lesser appreciated function of nitric oxide unfortunately up to this point is its anti-oxidant property or function, which I will come to that a little bit later on.

So if you want to summarize considering the safety of these products, really there are two

issues or two problems that you need to keep in mind, which makes the hemoglobin solutions unique and rather different from any other biologics that really we deal with.

To start with, the first issue or the first problem really lies within the product itself, the hemoglobin. Hemoglobin, unlike any plasma or blood-derived product we deal with, exists in different forms and states. It does not remain in the same form and shape that you really infuse the patient with. The first of these forms that we would like to keep the hemoglobin in all the time is of course the ferrous or the functional form. This is the form that reacts and carries oxygen and this is the form that obviously if it was close enough to the NO binding, NO production site would react with NO more avidly than its reaction with its natural partner, the oxygen. Hemoglobin in these two processes are spontaneously auto-oxidized to form the non-functional form of the hemoglobin, which is the second form, the ferric form. Nitric oxide reaction immediately will give you methemoglobin. The question is how much methemoglobin is too much? This is an important question that has been addressed by very few studies, one of them actually by Dr. Gus Vlahakes, who is with us today. A few years ago, he

used in his sheep model of exchange transfusion, and I believe the hematocrit in these animals were brought down extremely low. He infused these animals with polymerized hemoglobin, bovine hemoglobin, with a glutaraldehyde polymerized hemoglobin. And he actually took the bother to measure in the serum of the animal the transition of hemoglobin to met. And he reported that in the first 24-hour, the initial methemoglobin of the initial solution from 3 to 4 percent went up to 39 to 40 percent in the first 24 hours.

This question was also more recently addressed by Robert Shore from ENZON. He actually increased in the initial solution, which is pegylated hemoglobin in this case -- he used different solutions with a different amount of methemoglobin. He started from 5 percent to 50 percent. What he concluded from that study basically -- and they looked at the tissue oxygenation. They concluded from that study that anywhere between 10 to 15 percent of your solution turning into met will seriously compromise the ability of hemoglobin to deliver oxygen.

The other form of hemoglobin that if it is left alone in confined spaces in the vasculature or somewhere else, hemoglobin can actually turn and

now become even higher in terms of oxidation, which is quite a toxic form of the hemoglobin know as the ferryl. This issue is being dismissed for a while as purely academic work left for those of us who deal with hemoglobin. But actually in recent months, it was reported that this particular form of hemoglobin was detected in animal blood and human blood. The point here I am trying to make is very simple. This is the product that you deal with that keep changing, and these transformations, as they happen they change the hemoglobin from totally functional to less functional and in some cases, providing the right conditions, you can actually turn it into a toxic product. The good thing about all of these is that now we know so much that we can actually manipulate and control these reactions. Once we understand, which we do now, the mechanism underlying these reactions, potential manipulation of the ability of the hemoglobin to autooxidise or to be reactive can indeed be manipulated.

The second problem with hemoglobin is of course the neighborhood or the locality that the hemoglobin finds itself in, and that is of course the vasculature. This is a general vasculature bed. Obviously, we do realize that the beds are different and they are under different control mechanisms.

Generally, of course, it is accepted now that nitric oxide is produced by the endothelial cells and diffused at the lumen or to the subendothelial spaces to trigger a cascadive reaction, leading ultimately to the vasodilation of the vascular system. What has emerged in recent years is the fact that NO has another additional useful purpose to be there, and nature had to balance between nitric oxide and other oxidants such as superoxide. These are kept at bay by the enzymes that are capable of scavenging this. Once you have this balance under normal conditions, the possibility of oxidants produced in the vasculature is obviously minimized. When you have hemoglobin there, the situation will obviously be different. And also, when you encounter a situation where the vasculature system itself is compromised -- a number of conditions, anywhere from diabetes to ischemia and sickle cell and a number of other conditions that are known from the NO point of view that the vascular system is actually compromised -- what you see is this imbalance. There are more of these oxidants and less of the NO and hence we lose that anti-oxidant property of hemoglobin -- or rather of nitric oxide.

The question is now the size of the hemoglobin. If we increase the size of the

hemoglobin or we leave these tetrameric. Which one can do more harm, if you like. There are a couple of points or papers which came out very recently which really address these issues and that we need to bear in mind. One of them is the intravascular flow of the vasculature here causes the reduction in the ability of red cells to consume nitric oxide, and this is good in a way. What happens there is you create a nitric oxide free zone, an RBC free zone. In other words, the red cell really does not reach these parts where NO is produced. There is a minimal amount of NO scavenging there. The intravascular flow does not influence hemoglobin, cell free hemoglobin, which means hemoglobin can easily reach to this area of the vascular wall, within very close proximity to the NO, considering of course the NO half-life and the area that is covered. It could easily reach there.

Somebody also calculated more recently that if you have free hemoglobin here, it will react with nitric oxide almost 500 times more than the same amount of hemoglobin encapsulated within the red cell, which confirmed the earlier suggestion. Which means you really need to somehow stop the hemoglobin or encapsulate the hemoglobin if you want to prevent the interaction between the two, vasoconstriction or

hypertension.

Again, like I said, this is still an open debate. A couple of experiments, again, in recent years. One particularly interesting study can from Ann Baldwin's lab where she used the mesentery system. She used two hemoglobins, small diaspirin cross linked hemoglobin and pegylated hemoglobin. And what she finds here is basically albumin was leaking through the gaps between the endothelial cells. The interesting thing is this phenomena is very similar to a phenomena that she had of the unpublished when she used NO synthase inhibitor. So clearly the size is important, but also the proximity of these proteins to the NO site could be an important issue.

So what are the questions that I and many other people in the research community have in mind now and what keeps us really sort of thinking about these projects are more down-to-earth questions from a regulatory point of view will be obviously addressed and presented a little bit later by my colleague Toby Silverman. But the questions that I have and many other people in the research community are really basically these. Are these toxicities particular to all classes of compounds or do we have to start really seriously thinking about the size of

the protein and other important properties that have been ignored for a while. These are rheological and oncotic properties. Remember, these hemoglobins, in spite of their differences in size, they also do have because of the surface decoration or the polymerization, they do exhibit different oncotic properties. Do we need also to consider that? And how these properties put together will impact the clinical outcome of a trial. The heme mediated toxicity that I have just spoken to and, again, like I said has been sort of put aside for a while, such as the oxidation and the NO reactivity -- these reactions that I have mentioned just now, will they really be limiting in ultimately having a useful blood substitute? And how are we going to ultimately balance the redox chemistry and vaso-reactivity of these products? Will we just simply tolerate them or will we demand to actually control them and lessen the severity of some of these side reactions?

I think that is about all I have to say in these 20 minutes. Like I said, if you have questions, maybe after Dr. Toby Silverman, we will have 5 or 10 minutes for that. In the meantime now, I have asked Dr. Toby Silverman, who is a medical officer in the Division of Hematology.

DR. SILVERMAN: I want to acknowledge all of the people who have worked in this area. In particular, I would like to acknowledge Dr. Fratantoni, whose 1994 "Points to Consider" -- I know that he was the major author -- I went back to over the weekend to look at. And I realized that the talk that I have given in the past and will repeat today falls very much in line with what was written in 1994.

In November of 1998, I presented two talks. Most of the people in this audience or many of the people in this audience heard the second of them. The first of them was a talk in San Antonio at the Association of Military Surgeons of the United States at the request of the Army. I embellished and enhanced that talk a little bit later that month at an IBC conference. Since that time, the points that were made in those talks have formed the basic framework for many of the considerations for clinical trials now being discussed. At the end of this presentation, I will present the questions for the panel.

In September of last year, an Institute of Medicine conference was convened to review the state of the art of fluid resuscitation to identify targets for therapy and to make recommendations for

future research directed at the acute treatment of massive blood loss on the battlefield. This conference was convened at the request of the Navy.

Now my talk today and in the past comes out of a review of discussion points at the meeting held by the Institute of Medicine in 1998. As I said, a subsequent talk at the IBC meeting in November expanded on the discussion to instances of civilian trauma and to continue the discussion about the design of clinical trials in elective surgery.

I want to remind the audience -- some of you have heard this before but some haven't. Blood substitutes, so-called, and oxygen therapeutics, so-called, are biological drugs or drugs. I want to clarify that when I use the term blood substitutes, I certainly don't mean to imply that any of the products under discussion today can actually substitute for all of the properties or activities of whole blood or packed red blood cells. Rather, I mean to say that these products have been designed to substitute for or imitate the oxygen carrying and delivery capabilities of blood, and that is the subject of today's conference.

Now nature has evolved a very elegant transport and delivery system. We are only now, as discussed by Dr. Alayash, beginning to understand the

important nuances of that system. The ability of products in development to perform those tasks effectively and safely is not assumed and will be the subject of ongoing clinical trials which are the subject of discussion today. Now it has been said -- perhaps not so much recently but certainly over the past year -- that trials now are larger than typical for biological products. Most biologics approved to date have been for relatively small patient populations. There are, however, some exceptions to this. For some indications for some biologics, studies have included several hundred and indeed several thousand patients per cohort. There is no fixed rule about sample size. Sample size is heavily dependent upon the anticipated risk/benefit profile. Large sample sizes are generally needed to permit adequate assessment of the risk as opposed to the benefit of drug use.

What are the general efficacy considerations for drugs? The endpoints listed here are to be distinguished from drug activity endpoints. General efficacy considerations include, most importantly I think, an increase in survival, a prevention or slowing of disease progression, a decrease in morbidity, or measurable symptomatic relief. Drug activity is measured as results

obtained in a biological or chemical or physical assay, either in-vitro or in-vivo. On occasion, such activity endpoints have been used as surrogates for efficacy, so it becomes necessary to define the term surrogate.

A surrogate endpoint or marker may be used to diagnose disease or evaluate patient response to treatment. A surrogate marker should reflect what is happening in the underlying disease. The relationship between the surrogate and the true endpoint of interest should be such that an effect on the surrogate marker reflects an equivalent effect on the disease or the true clinical endpoint of interest.

Now we have put out a position -- FDA has put out a position that use of any surrogate endpoint or endpoints, such as blood pressure, lactate levels, base deficit, oxygen consumption, tissue oxygenation, or organ functional assessments must be validated as correlating with survival -- in hemorrhagic shock, exsanguinating hemorrhage -- before use in lieu of a mortality endpoint. Now, there are other arenas where oxygen therapeutics are going to be used, and the same statement pertains that use of any surrogate endpoint will need to be validated for use in any other clinical trials as well.

Now what are some of the other efficacy considerations for trauma? Evaluation of so-called blood substitutes in cases of blunt and penetrating trauma. FDA anticipates that mortality will be the endpoint of choice for clinical trials in hemorrhagic shock or exsanguinating hemorrhage. The reasons are as follows. If administration of a resuscitative solution resulted in worsened mortality, then I think all would agree that efficacy would not have been demonstrated. If a resuscitative solution neither improved nor worsened the survival, nor improved a major morbidity, I think then efficacy would not have been demonstrated. If a resuscitative fluid does not worsen mortality but results in a major irreversible morbidity to those who did survive, then I think also efficacy would not have been demonstrated. Now if a resuscitative solution improves survival, but at the expense of a major morbidity that impacted permanently on a person's ability to function, then I think efficacy will have been demonstrated in that the mortality endpoint will have been met. But there is in fact a larger societal question of the quality of the life saved, and this will require discussion. This is outside the purview of the FDA. This is a larger social question.

It is very important to remember that in

many situations, particularly in field settings, many more people will be exposed to a product than the population potentially helped by administration of the product. Ability of the EMT, or for that matter the combat medic in military trauma, to triage those who might benefit from those unlikely to benefit will probably be very limited.

Now if a resuscitative solution is not anticipated to improve the mortality associated with trauma, then the ability of such a product to improve a major morbidity can be used to demonstrate efficacy of the product for use in trauma. The product should have an effect on a serious morbidity that has substantial impact on day-to-day functioning. An impact on short-lived or self-limiting morbidity will usually not be sufficient. But the morbidity need not be irreversible, provided it is persistent or recurrent.

As with the mortality endpoint, use of any surrogate endpoints must be validated as correlating with improvement in a major serious morbidity before use in lieu of the morbidity endpoint.

Let's move to some consideration of field use. Field use, either civilian or military. Studies in circumstances where blood is not routinely

available, such as in ambulances, hospitals lacking a blood bank or ready access to a local blood center. There will need to be studies in situations where blood is available but with randomization of study subjects to drug or blood. These various scenarios speak to very different risk/benefit assessments. Where blood is routinely available, use of one of these products should certainly not worsen mortality. Morbidity associated with product use will require careful assessment and quantitation. We will return to these points when discussing perioperative use.

It is not clear whether the results of studies under relatively controlled situations, as in the emergency room, could be extrapolated to field situations, either civilian or military. And it is not clear if efficacy in case of civilian trauma could be extrapolated directly to efficacy in combat situations where there is prolonged delay to definitive care, where the care occurs under adverse conditions, both environmental and physical, in uncontrolled circumstances, and where there are limited monitoring and therapeutic resources.

This conference is co-sponsored by the Department of the Army, and I would like to talk a little bit about combat casualties. Worldwide approximately 20 percent of soldiers wounded in

action will die. 90 percent of combat mortalities occur even before entry into the medical system, 80 percent within 30 minutes of the injury. 50 percent die as a result of massive blood loss, 25 percent due to surgically uncorrectable torso injury, 10 percent due to otherwise surgically correctable torso injury, and 9 percent due to peripheral injury.

Penetrating trauma is the major cause of combat casualties, both in the past and at the present. The increasing use of more effective body armor has actually resulted in an increase in the percent of casualties suffering from blunt trauma as opposed to penetrating trauma. 10 percent of the mortally wounded do survive to enter the medical system. These patients die from results of hemorrhagic shock, head injury, or contamination from the GI tract. The main focus of military trauma care during the 20th Century has been on this 10 percent of the wounded who actually enter the medical system. 24 percent die of hemorrhagic shock, 43 percent die of head injuries, and 12 percent die of septic shock.

Before embarking on an evaluation of efficacy of any of these products in the trauma setting, FDA believes that products should be evaluated in Phase II studies under more controlled

conditions such as elective surgery. Such studies also provide a basis for evaluation of products for perioperative use in Phase III. In Phase II, one can examine the hemodynamic effects and the toxicities of the various products, gain a preliminary estimate of the maximum tolerated dose, and a preliminary evaluation of toxicity at that dose, and an evaluation of drug activity for temporary reversal of physiologic transfusion triggers.

Moving to the perioperative use. Up until this point, I have talked about circumstances where one of the products might save a life. Under such conditions, it is pretty clear that the risk/benefit paradigm shifts very heavily toward efficacy. I guess it is a truism to say that the better the product at saving lives, the more obvious the clinical benefit. While it is true that the efficacy of blood has never been demonstrated in a rigorous clinical trial, the utility of blood in treating life-threatening anemia I think is not in question. The historical data base from the period prior to availability of blood answers I think that question resoundingly.

There are, however, many considerations to keep in mind, and Dr. Klein has outlined those very nicely in his talk. These considerations

include the known risks associated with the use of blood and then the unknown risks associated with the use of blood, including emerging infectious diseases.

Because of this recognition, FDA has agreed to accept reduction or avoidance of allogeneic red blood cell usage as an endpoint for clinical trials. FDA is not asking companies to measure the number of permanent adverse outcomes attributable to blood usage in a clinical trial. I think from the numbers you saw this morning, it would be pretty clear that such a demand would necessitate enormous studies. However, we need to recognize that reduction in or avoidance of allogeneic red blood cell usage is a surrogate for reduction in the risk of allogeneic red blood cell transfusion. I need to emphasize also that avoidance of allogeneic red blood cell transfusion does not equate to avoidance of all allogeneic risk. It is anticipated that traditional transfusion triggers will be used for licensure of early stage products. The reason for that is as follows. FDA is not asking companies to measure oxygen delivery capabilities of these products directly in the efficacy endpoint, as such an evaluation would require development of a new potency assay to reflect the oxygen delivery

capabilities of the product in-vivo for those biologic products subject now to BLA, biologic license application. As well as the development of new transfusion triggers otherwise known as dosing guidelines.

So what does FDA ask? FDA does ask that sponsors evaluate the safety profile of the products. Again, more patients are likely to be exposed to the product and blood than are anticipated to benefit from avoidance of an allogeneic transfusion. Again, avoidance of an allogeneic red blood cell transfusion does not equate to avoidance of all allogeneic risk.

FDA believes that contrary to clinical trials for most other products, clinical trials for these products capture efficacy data in the safety endpoint. Many of the adverse events for the hemoglobin-based oxygen carriers in particular have been thought to have occurred as a result of the vasoactivity of the product as described by Dr. Alayash. They may also have occurred as a result of inadequate or inappropriate offloading of oxygen resulting in tissue ischemia. Adverse events may be either new and unanticipated or be of the type reported to be associated with the different forms of either the hemoglobin-based oxygen carriers or the perfluorochemical-based emulsions. Adverse events

reportedly associated with use of the hemoglobin-based oxygen carriers overlap with adverse events known to occur perioperatively.

Therefore, FDA believes that studies should be powered for safety as well as for efficacy, and that safety endpoints should be defined prospectively. Since adverse events are likely to increase with increasing dose of product administered, FDA will ask that the number of oxygen carrying units of both product and blood be reported.

This slide will be the subject of some discussion today. It is anticipated that adverse events leading to permanent morbidities will be the primary safety focus of clinical trials for perioperative use. The extent to which these types of adverse events will be evaluated will depend on the rate at which they occur in the comparator group. If in the comparator group such events are very rare, then evaluation of series adverse events may suffice.

For purposes of data analysis, FDA suggests blinded review of all new and novel adverse events and predefined categories of adverse events with a data safety monitoring board that is blinded to treatment allocation. FDA recognizes the tremendous difficulty, particularly for the hemoglobin-based oxygen carriers, in conducting

double blind studies. FDA also recommends a blinded determination of serious adverse events leading to permanent sequelae, again by a data safety monitoring board blinded to treatment allocation.

FDA recommends prospectively defined safety stopping rules. FDA anticipates that clinical trials for perioperative use would be stopped early and unblinded only for safety considerations, particularly permanent morbidities, rather than for the efficacy endpoint.

Sample size calculations, safety boundaries and statistical analyses will be the subject of negotiations between manufacturers and FDA. Now we have a number of questions for the panel, and I would like to go over these. These are included, I think, in your packets that you all received. I would like to read them and then we will have them on overheads during each of the subsequent sessions.

For safety, toxicities and laboratory findings that are known or thought to be associated with hemoglobin-based oxygen carriers include cardiovascular and hemodynamic effects, immune cell activation, neurotoxicity, changes in coagulation, gastrointestinal changes, free radical generation, and decreased post-resistance to infection. These

have all been very elegantly summarized by Dr. Alayash in his talk.

He has also summarized the adverse events that are known from the literature for the perfluorochemical emulsions, and those will also be the subject of discussion. The questions are as follows. Are there any potential toxicities that should be added to this list? Which of the listed findings is potentially clinically significant? Does the use of oxygen therapeutics affect the incidence or susceptibility to or the severity of systemic infection? What evaluations should be included in the safety component of a clinical trial?

For the trauma session, should mortality be the endpoint of choice for clinical trials in hemorrhagic shock or exsanguinating hemorrhage? Are there any endpoints that could serve as surrogates for mortality? What would constitute satisfactory validation for such endpoints if it is decided that there are? Are there any endpoints that are acceptable in the face of an adverse mortality outcome in trauma? Could the product have an effect on a serious morbidity that has substantial impact on day-to-day functioning? Are changes in morbidity scores, such as APACHE, an appropriate measure of morbidity outcomes? Where blood is not available,

should the product be tested in actual acute blood loss situations to demonstrate an impact on survival? To what extent can data generated in an ER or OR setting be extrapolated to the rural setting? Are clinical trials in a rural setting necessary to demonstrate efficacy and safety in settings where there is delay to definitive care? Are trials in the ambulance setting necessary? Again, where blood is not available, to what extent can efficacy demonstrated in clinical trials of product use in cases of civilian trauma be extrapolated to efficacy and safety in combat trauma? For trauma, again, where blood is available, can clinical equivalence in mortality between an oxygen therapeutic and blood be a basis for licensure? If yes, what lower 95 percent confidence interval for mortality rate would be acceptable?

In elective surgery, should an oxygen therapeutic be evaluated in controlled clinical trial or trials in hemodynamically unstable patients requiring blood? Should that trial be done prior to licensure for elective surgery to ensure that use in surgical patients at the highest risk would not lead to a worse outcome than if blood were used? Should an oxygen therapeutic be evaluated in the surgical setting with a high degree of patient risk to assess

whether those risks are increased by the use of the product?

Finally, FDA has proposed that studies be powered for safety as well as efficacy and that safety endpoints should be defined prospectively. If a sponsor is conducting a single pivotal trial in a stable, elective surgery population, what safety endpoints are most likely to predict adverse events in patients at higher risk? Based on the available safety data, what safety endpoints should be required?

I wanted to add one comment, because we have had some comments about the issue of informed consent. Informed consent is outside of the purview of this particular workshop. We assume -- and I think we should all assume that any clinical trials that are done will be done with the appropriate informed consent mechanism, whether that is a written, explicit informed consent or implied. We don't have the experts here to give that particular topic any kind of in-depth discussion. Thank you.

DR. ALAYASH: We have about ten minutes before we break. Again, unfortunately, we don't have the microphones on both sides. So let's try this. If you have a question, jot it down on a piece of paper and pass it to Beth or Felice, and write down

the name of the individual it is addressed to -- myself, Toby or Dr. Harvey Klein, please. Again, we have about 10 minutes before we break. Do you see anybody writing anything? Do you want to try to shout your questions out? No? It has to be written. Okay, I guess we will have to -- oh, we have one. Dr. Harvey Klein, could you come up here, please?

DR. KLEIN: The question looks like it is blood supply problems in the UK, what are the clinical consequences? This has to do with the recent decision of the FDA based on a number of advisory committees to restrict donations from donors who have spent six months or more in the UK over the past -- between 1980 and 1996. We don't really know what the impact is going to be. Data from the Red Cross suggests that at least 2 percent of the donating population is going to be rendered ineligible indefinitely. The apheresis platelet donors, it appears that that might be even more. That is going to have a significant impact on the availability of blood in the United States. 2 percent doesn't seem like a very large figure. But if one looks at the data for current availability of blood and current utilization, they are tighter than ever before, and there is at least a prediction from the only source of data available in the United

States on both utilization and availability that sometime in the year 2000 or shortly after that, the line of availability and utilization will cross. Whether that will actually happen I think remains an area of some question. But a 2 percent reduction in available donors certainly is not going to help. I hope that answers the question.

DR. ALAYASH: Okay. I have a very long and complicated question, but I think I can understand the gist of the question. The question is from Dr. Simoni. I think the question is related to what extent the redox chemistry of a particular hemoglobin is related to inflammatory response or inflammatory reactions. I am not really sort of -- you need an immunologist to answer that. I don't really have the appropriate answer to that. But clearly the redox chemistry of hemoglobin, because of its ability to interact with a number of components in the blood, I wouldn't be surprised if this sort of reaction could have something to do with that. Other than that, I don't really have any specific answer to that in terms of concrete chemistry. Any more questions? If not, then I think we will go for the break and we will be here back around 10:00, please. Thank you.

(Whereupon, at 9:26 a.m. off the record

until 10:02 a.m.)

DR. AEBERSOLD: We are going to get started, please. The coffee break was a minor catastrophe. They ran out of caffeinated coffee and some of us only had decaf available. But we will carry on as best we can. Can we get the session started, please? The next two hours we will have presentations from several different manufacturers of blood substitutes. These are, by the title of the session, manufacturers experienced in advanced clinical trials. We have asked those companies which have conducted fairly large or moderately sized, I should say, clinical trials past the early initial Phase I trial. So the emphasis here on advanced is trying to collate data past the anecdotal episode stage. We have asked the manufacturers to speak very specifically to the safety profile of the products and the safety concerns that have been identified in the clinical trials so far.

Before we get started, I have one announcement. Dr. Michael Beauchamp, there is a message for you. Pick it up here. It is said to be urgent. And if there are other messages, I am told that they will be on the registration table. If anybody wants to or is expecting a message, they can check there for messages.

The structure of the session will be we have asked Baxter to speak at greater length because of the Phase III trial that was conducted in trauma, which was halted early. And we would like them to go into some depth on that experience. The other sponsors will have 15 minutes or so. My unhappy chore is to be the timekeeper and to remind them when their time is up. Then after lunch, we will have an hour for questions to the manufacturers. It is listed as panel discussion and questions addressed to the manufacturers. We will actually ask the manufacturers to come up so they all have microphones. So this morning, if there are any very quick questions of clarification, we will take those after each talk. But remember there is going to be an hour this afternoon. We figure that anybody who has a question can come up and use the end microphone on the table this morning.

So the first speaker is Dr. Michael Saunders, who will be talking about clinical experience with first generation hemoglobins. I will put the message for Dr. Beauchamp out on the table.

DR. SAUNDERS: Thank you, Dr. Aebersold and Dr. Alayash and distinguished members of the panel. On behalf of Baxter Hemoglobin Therapeutics, I would like to express our sincere appreciation for

the opportunity to share our clinical research experiences that we had with the hemoglobin compounds.

I am sure you are aware of the outcome of our clinical development program with the termination this past year. And while disappointing, we still learned a great deal about administering hemoglobin and conducting clinical trials in a variety of indications.

My presentation is designed to provide an abbreviated description of the highlights of that experience. I'll do this with a brief review of the history, a review of the key Phase III clinical trials, a summary of the clinical safety experience. I will provide or propose an interpretation of those findings, and I'll identify some important clinical research lessons learned. Finally, I will share a summary of those experiences.

To begin with, I would like to define the principles in this discussion. DCLHb or HemAssist is diaspirin cross linked hemoglobin, and this was the subject of the Baxter clinical development program. I will just briefly touch on rHb1.1 or Optro, which is dialpha recombinant hemoglobin with a genetic modification to improve oxygenation. This was the subject of the clinical trials, the clinical

development program at the former Somatogen. And lastly, for our purposes, I would like to distinguish first generation hemoglobins as those with nitric oxide binding kinetics of native human hemoglobin.

With that framework in mind, I will go on to some of the historical perspectives and the overview. The anticipation of the clinical utility of DCLHb was built upon an extensive preclinical evaluation involving 15 animal species, which demonstrated that the product was safe, stable, and had no particular immunologic or coagulation disturbances. There was no evidence of accumulation and no nephrotoxicity. There were, however, some findings, as Dr. Alayash had mentioned earlier, of the hemodynamic effects that we were able to demonstrate in the preclinical species as well as some moderate GI symptoms and some enzyme elevations that were seen.

With this experience, this led into beginning the clinical trials. In the early clinical trials, we again demonstrated the vasopressor effects, confirmed those findings in man, as well as demonstrating enhanced tissue oxygen consumption and extraction. There were a number of features of the results of these trials which led us to the promise that the product could be useful in a number of

clinical indications and therefore was encouraging. We did use low doses with a slow escalation process with respect to the clinical safety concerns. The overall sum total of the experience, though, was that the product was well tolerated.

So in conclusion from those early trials, we confirmed the potential usefulness and safety of going forward with further development.

The first Phase III clinical trial was performed in cardiac surgery patients performed in Europe. It was a single blind study and was designed to evaluate the endpoint of spared transfusions through 7 days or the end of hospitalization. 209 patients were enrolled in the study. It is important to note that this was a low dose by comparison. We are talking about three units of what we call a unit of DCLHb, which is 250 cc of a 10 percent solution or 25 grams. This was compared against packed red blood cells.

The study demonstrated a benefit. We were able to show avoidance of packed red blood cell transfusions at a rate of almost 60 percent at 24 and continuing to a level of about 20 percent at 7 days. While this is a decline, we still felt that with enhanced experience of investigators and clinicians, this may actually demonstrate a potential that the

product can delay the decision to transfusion and ultimately result in greater avoidance of transfusion.

I would point out that the mortality rate was balanced in this trial. Adverse events were greater in the DCLHb group compared to the control group. I will come back to that a bit later because this has a feature that we believe is related to the single blind nature of this trial.

This trial was also the basis for a European submission for approval in April of 1997, and it gave us the experience of regulatory review. We received extensive questions and the process of responding to those questions was ongoing at the time of the termination of the program last year.

The companion Phase III trial done in the surgery setting was the U.S. perioperative trial. By distinction, this was a double-blind trial. While requiring complicated measures and a lot of consumption of resources, this was performed successfully. The endpoints were very similar to the cardiac surgery trial, seeking evidence of avoidance or reduction of blood transfusion through 7 days. 181 of the anticipated 400 patients designed for this trial were enrolled. Again, there was a low dose administration.

In the results of this trial, we did see evidence of the avoidance and reduction of packed red blood cells. Furthermore, as far as other blood products were concerned, we saw an overall use reduction of over 40 percent, and this was represented primarily by a reduction in plasma and equivalence as far as platelet administration was concerned. This study was suspended after two serious adverse events were noted that did have some similarities with events that had been reported to the agency. Even though the data monitoring committee -- the data safety monitoring committee for this trial advocated that we continue the study, this was also terminated with the rest of the program last year.

In addition, we saw the hemodynamic effects that we have talked about earlier. Here is an illustration of those numbers. The mortality was balanced between the treatment groups. And importantly, in this trial we saw an insignificant difference between the SAE and AE numbers between the two treatment groups, and we feel that this is related to the double blind nature of this trial compared to the cardiac surgery study. We saw evidence of increased vigilance on the part of the investigators to report serious adverse events and

adverse events with the active treatment group as opposed to the control group in this situation.

We also saw a number of serious adverse events that appeared unusual or unexpected for the clinical setting, including systemic inflammatory response syndrome, adult respiratory distress syndrome, multi-organ failure, among others. And I will come back to that in our analysis of some of the overall clinical safety concerns.

A landmark study was the U.S. trauma trial for the clinical development program with DCLHb. Landmark from the standpoint both for the tremendous effort required to develop and design the trial, but also being the first to utilize the exception to informed consent. Unfortunately, it was also the keystone to the eventual outcome of the program with DCLHb.

This was a single blind study and the primary endpoint was looking at 28 day mortality. 98 of the expected 800 patients were enrolled in this trial, and importantly, I want to emphasize that the predicted mortality rate for this patient population based on historical controls was 40 percent. This was still a relatively low dose, particularly considering that these are patients in severe shock.

The key findings were clearly the

imbalance in mortality that was seen in this study, highly significant and unfavorable for DCLHb. But I want to point out that in this population, which we predicted to have a mortality rate of 40 percent, the control group actually had a mortality rate of 17 percent. That was surprising to us and does have an important learning in the process.

As a result of these findings, there was a premature termination of this trial. The data monitoring committee made the decision that based upon the imbalance in the mortality as well as the futility of reaching a mortality efficacy outcome that the trial should be terminated. There was an exhaustive search for any correlations to the mortality, and the bottom line was that we failed to demonstrate a clear reason or a clear explanation for what happened in the U.S. trauma trial. We did find some troubling observations, though, which included an imbalance in the prehospital cardiac arrests and traumatic brain injuries, many more in the DCLHb group compared to the control group. There were also evidences of randomization and treatment bias reported in the studies. An example is illustrated by the intent to treat patient population aside from the treated patient population had a much, much higher mortality rate in the control group than in

the DCLHb group.

The companion trauma trial was the European trauma trial, also known as HOST. This had a couple of important distinctions compared to the U.S. trauma trial. We were looking at morbidity as opposed to mortality as a primary outcome. This was also an earlier interventional opportunity. In Europe, physicians ride in the ambulances and this is an opportunity for enrolling the patients on-site or on-scene and being able to administer the product immediately.

There were 121 of the expected 400 to 800 patients enrolled in this trial. Again, a low dose of administration. What we found was actually a near equivalence of the number of deaths between the two treatment groups, although there was a slight trend for the mortality rates to be higher with the DCLHb group compared to the control group.

There was no evidence of efficacy as far as the organ failure scores were concerned. We saw no evidence of increased hemorrhage. Serious adverse events were similar between groups. There were somewhat more adverse events with the DCLHb population. Pancreatitis was seen in the DCLHb group and not in the control group, but the majority of these were clearly trauma-based -- based on either

clinical findings or imaging studies.

So to summarize the clinical safety, I would first want to illustrate the extent of exposure that we saw throughout these studies. Altogether in patients and volunteers, we evaluated over 1,150 patients. I would also want to point out that had the Phase III trials been allowed to continue to their normal conclusion, this number would have been approximating 2,500 patients.

So the bottom lines are that there were large numbers of patients studied. There was a variety of indications represented here. And there were four Phase III clinical trials evaluated. We did see an imbalance in the serious adverse events, greater numbers for the DCLHb patients than for the control patients overall. But again, as I have pointed out, this we feel is perhaps related to enhanced vigilance in the unblinded trials. Certainly with the unfavorable mortality outcome in the U.S. trauma trial, there is always a concern to wonder about mortality in other studies and across the program. And indeed in the control trials, there was a greater number of deaths in the DCLHb population compared to the control population. Actually, the number is 16 greater. This actually turns out to be exactly the increased number of

deaths in the U.S. trauma trial. The take-away message here is that throughout the remainder of the program, there was balanced mortality across studies. It was only in the U.S. trauma trial that we saw the imbalance. This is the outlier.

So I mentioned early-on some of the serious adverse events that were unexpected in the U.S. perioperative study. This prompted an internal review initiated by Baxter to try and understand some of the findings. So there was a clinicians view and assessment of unexpected events for a given clinical setting taking clinical judgment into account. These were derived from the volumes of serious adverse event narratives that had been collected.

What I present here is a listing of some of the targeted serious adverse events that were tallied into this list. Importantly in italics I have emphasized those that did have evidence of imbalance, greater numbers for the DCLHb group compared to the control group. This includes ARDS, SIRS, multi-organ failure, pancreatitis and myocardial ischemia. Interestingly and importantly, I want to point out that there were some significant absences from this list including acute renal failure, hepatic failure, mesenteric ischemia, sepsis and rhabdomyolysis.

This was an interesting analysis, and what this exercise appeared to tell us was that there seemed to be a clinically meaningful increase in the number of events for DCLHb compared to controls. A notable increase in the events that I mentioned, and in sum total perhaps a 4 to 5 percent increase in the number of events, greater for the DCLHb, and interestingly also for Optro. A parallel experience with Optro here as well. Although I would also mention that these are after-the-fact observations, and it is not clear whether there is truly a relationship of these events to study drug. It is neither clear nor established.

To summarize this experience, I would want to say that we did demonstrate evidence of benefit with respect to sparing blood transfusions in the U.S. perioperative trial and confirmed by the cardiac surgery trial results. This may, in fact, lead to a concept that the product may be useful as a bridge to transfusion. We did also see the unfavorable mortality imbalance in the U.S. trauma trial. No efficacy in the HOST trial. And with the first generation recombinant hemoglobin, we saw a series of life-threatening serious adverse events in the cardiopulmonary bypass setting, which had some interesting parallels to the experience with DCLHb.

An assessment and interpretation that I would perhaps propose here is that nitric oxide binding may lead to microvascular effects which then subsequently goes on to a cascade of vascular inflammatory effects progressing to multi-organ failure.

Faced with these findings, Baxter made the difficult decision to discontinue the clinical program in September of last year. So with that information in mind, I would now like to turn attention to just a brief discussion of some of the important clinical lessons learned, if you will, and to begin with an overall view of the clinical development.

We know that it is essential to establish a preclinical/clinical link in study designs. That is to say that the preclinical models must more closely mimic or approximate the clinical situation. We also recognize that logical progressive development through the typical clinical phases is necessary. There are penalties for shortcuts. We learned that Phase IIB trials can be extremely helpful to sort out trial design and conduct issues. And as I am talking about trial design, I would want to point out that there were a number of lessons learned here as well. I mentioned the imbalance in -- or rather, the excess number of serious adverse

events that were seen with the DCLHb group in that unusual unexpected events category. We take away from this that a large number of patients are required to convincingly demonstrate whether or not that actually exists.

Blinding de novo is a desired characteristic of clinical trials. But we also recognize that it is not always feasible. The blinding we feel is in contrast to the customary considerations of blinding where peer reviewers and regulatory reviewers are concerned that there may be an unfavorable balance toward the active treatment. We actually saw an increased diligence for the investigators to report the adverse events more rigorously with the active treatment group. Concurrent controls are needed. I illustrated this with the U.S. trauma trial and the unexpected surprising finding of the control mortality rate being less than half of the actual concurrent control evaluated in this trial. There was also a tremendous amount of heterogeneity and variability observed throughout the conduct and execution of these trials, which led us to the feeling that we need to standardize procedures and decision criteria in the protocol. Efforts need to be made to reduce the investigator treatment and randomization bias, and

this would be done through more clearly defining patient inclusion/exclusion criteria, establishing perhaps a central randomization scheme. Selection or prediction of events and endpoints needs to be incorporated into the protocol. And then there needs to be a greater diligence with execution discipline and the monitoring of the trial. We also learned obviously about the hazards of performing trials in high risk populations.

Now with respect to the endpoints, mortality outcomes, I am very happy to see that this is a significant focus of the questions addressed to the panel. While mortality outcomes can be definitive and unambiguous, there are still a number of issues related. I have addressed the hazards of the high risk populations. We also saw in our clinical trials in trauma a bimodal distribution of patients, that is, an excess number of patients who are either so severely injured that mortality was an almost certain outcome contrasted with a population of patients who had such mild injury that it was unlikely that they would die at all. So the middle ground, those patients where the treatment may actually have an impact, was actually the least represented in the patient population.

There are a number of issues around

feasibility of doing mortality outcomes, including consideration for the treatment, the time frame and the design of the trial. It may create unrealistic expectations on the part of the study sites and study investigators. So I do applaud the notion of alternatively defining or accepting other outcomes, morbidity surrogates specifically.

And then finally, there are ethical considerations that we learned specifically with the waived informed consent.

So finally, I would like to summarize by saying that the first generation hemoglobins did develop a level of significant achievement of advancing to Phase III trials. I think this is a reflection of a certain level of safety and efficacy to get to this point. There were adverse events and outcomes observed, but low in frequency, and importantly they do appear to be attributed to mechanisms that we believe we understand and recognize. We also developed a greater understanding of the problems facing clinical development through this experience. Through it all, we have maintained great investigator and expert support and interest. And finally, I would point out that our conviction is that robust numbers of patients are necessary to establish the clinical safety and efficacy of the

hemoglobin products. Thank you.

DR. AEBERSOLD: Any immediate points of clarification type questions?

DR. KRUSKALL: I am Margot Kruskall from Boston. I'd like to ask you if you could give us a little bit of insight in retrospect as to which of your 15 animals and which animal models you think most accurately could have predicted what you found in the human trials, particularly as it relates to the vasoactivity of your compounds and also specifically the end-organ damage, for example the pancreatitis. Is there something that we can learn in retrospect as to where to focus models?

DR. SAUNDERS: Well, we are in that process right now of trying to fully understand that. My answer, I guess, would be that there are different models for the different problems that have been demonstrated. Certainly I am no expert in the preclinical setting, but the swine models for the cardiovascular endpoints are perhaps the most -- have been the most important for us. As far as the pancreatitis that you specifically mentioned, that is actually one of the more difficult ones to demonstrate in any animal species. So we have actually worked at trying to develop some provocative models.

DR. AEBERSOLD: The next presentation will be given by Dr. Peter Keipert from Alliance Pharmaceutical Corporation. The topic is clinical experience with Perflubron, an intravenous oxygen therapeutic, as a temporary red cell substitute.

DR. KEIPERT: I'd like to thank the organizers for the opportunity to give a brief overview of our product. Just by way of introduction, several of these issues have been nicely described this morning by Dr. Klein, and that is that blood inherently will always carry some risk. More recently, the focus now is on the supply shortages and that there are constantly pleas for more donation and delays in elective surgery. The third issue that we see around blood which wasn't described this morning is really the issue of the quality of that transfused product because of the storage lesion that occurs as these components, particularly the red cell, are stored over time. And this may be partly the reason why increased mortality was seen in the prospective study by Paul Lebert published in the New England Journal of Medicine.

Now the paradigm shift that has occurred several years ago in this field, and we certainly were a part of this since our product is white and behaves a little differently than hemoglobin, and

that is that originally everybody thought of these as large volume blood substitutes. Clearly these products have both blood half-life and dose limitations. And yet despite these two limitations, everybody in this field has been able to demonstrate physiologic benefits and some form of preclinical efficacy. Therefore, we now think of these products as temporary oxygen carriers.

Our approach, which we described about five years ago in 1994 at the previous meeting sponsored by the FDA, was the fact that your own blood is always the best, but in order to use your own blood, you need a method for that which is safe, effective, and can be done at a reasonable cost. Our approach has been to combine our product with an autologous method, thereby using the product to enable the autologous collection technology and maintain oxygenation at lower hemoglobin levels. By doing so, we make the patient their own donor. We increase autologous blood use and make it more efficient, and in doing so can minimize surgical blood loss.

What are the techniques currently available? There is autologous pre-donation, autologous blood salvage, and acute normovolemic hemodilution. And they are all designed by and large

to prevent the risks associated with blood transfusion. But there is a number of other features related to blood in terms of having a good quality, fresh product with platelets and coagulation factors. As you look down this list, you will see that only when you get to hemodilution can we really fulfill all of these potential desirable benefits of having that blood collected immediately at the time of surgery.

So why isn't it used more frequently if conceptually it seems to be such a good approach? The limitations are really two-fold based on efficacy. In order to make it efficacious, you have to be more aggressive and harvest adequate amounts of blood, and therein lies the safety concern. In elderly compromised patients, you don't know how well their cardiovascular system will respond, so there is a fear of taking away too much of their blood up front. If you look in the literature, there was a meta-analysis done and published in 1998. We don't have nice, large, prospectively-defined studies proving how this technique is efficacious.

So this is Alliance's combined approach. We coined this expression, augmented acute normovolemic hemodilution, and the cartoon simply illustrates that at the time of surgery,

anesthesiologists can now harvest several units of blood instead of the one or two that sometimes are routinely taken. The extra anemia now is offset by administering your oxygen carrier during the acute bleeding phase of surgery, and only once you've achieved hemostasis or you've achieved truly profound levels of anemia, now only do you start to reinfuse your fresh autologous blood to bring that patient back to a safe hemoglobin, and also to give them back all their platelets and coagulation factors.

This is a new method which is a combined approach. We believe that it can decrease the safety concerns, because you are now adding an oxygen carrier to this situation. And in doing so, you enable the anesthesiologist to now do hemodilution really the way it was intended to be efficacious, by collecting more blood and allowing that patient to tolerate the lower intraoperative hemoglobin.

This is what our product looks like. It is ready for use in the bottle. It is a milky-white emulsion containing 60 percent by weight of PFCs. This formulation is so stable in contrast to earlier first generation products like Fluosol, that we can terminally heat sterilize the product. We have very small particle size, about 40 times smaller than a red cell, and it has a shelf life expected to be

about two years. The unit dose, as shown here, contains about 65 grams of PFC. And based on some preclinical data and more recently data from our Phase IIB studies, we now know that this one unit has an equivalency in terms of its contribution to oxygen consumption of at least one unit of red cells.

In the interest of time, I think the focus at this meeting is more safety, so I won't show you any preclinical efficacy data. I'll just summarize the findings from many studies here. We have seen positive oxygenation signals, positive meaning that they go in the direction that you expect them to go in. When you put an oxygen carrier into the circulation and you don't metabolically disturb the system, you would expect your mixed venous PO_2 and mixed venous hemoglobin saturation to increase, and this has in fact been demonstrated both in animals and in humans.

Contrast to earlier reports in the literature on some of the other products, we do not have any adverse hemodynamic disturbances. No changes in cardiac output or vascular resistance and blood pressures. Using a variety of invasive, surface and penetrating needle electrodes, we have been able to demonstrate enhancement of tissue oxygenation in at least five different tissues. And

in several of these studies, we have been able to look at some index of organ function and have been able to demonstrate that the added oxygen that is being provided by the PFC is in fact utilized in some manner.

Now in terms of safety, the two biological effects that have been discussed in the literature and that we have studied very, very carefully -- these have been seen in preclinical and in human studies -- are a transient reduction in platelet count. This occurs several days after dosing. It is really due to the clearance and sequestration in the spleen of the PFC particles which interact with platelets, so you get some uptake of platelets in the spleen. The magnitude of this effect is dependent on the species. It is also dependent somewhat on the PFC emulsion formulation. The good news, though, is that it is a transient effect. Generally we have recovery to normal range by seven days. And very importantly, we have no effect on hemostasis. We have normal platelet function, normal bleeding times, and no adverse effect on marrow function in terms of producing new platelets.

Another effect that has been seen essentially predominantly in the conscious volunteer

or the awake subject are flu-like symptoms with occasional fevers which have a delayed onset at four to six hours. This is really a natural consequence of the macrophage mediated clearance of these emulsion particles from the circulation. And what we have learned is that this is significantly attenuated by decreases in emulsion particle size. Our current formulation, in contrast to our first generation formulation, has significantly attenuated these side effects. So that now if we look at our overall safety profile, we still see a mild reduction in platelet count. It is about a drop of 15 to 20 percent in the mean platelet count from baseline. We have some flu-like symptoms -- some nausea, headaches, and transient fevers in a fairly low percentage of subjects now because of the smaller particle size of our current emulsion formulation.

Again, in contrast to a lot of what is in the literature, both from earlier PFC emulsions and hemoglobin solutions, we saw no vaso activity. We have no suppression of immune function. We looked at this very carefully since these particles are taken up by the phagocytic cells of the immune system. In direct contrast to Fluosol, which uses a synthetic surfactant, in our product, which is lecithin based, we have no complement activation. We see no

impairment of coagulation. And as I mentioned, no effect on platelet function or bleeding time.

Overall clinical experience -- this is in Phase I and Phase II only. 540 subjects have been dosed and 340 have received drug. We have about a ten-fold dosing range in terms of active drug, anywhere from a half a unit to approximately five units of product. Here you can see the breakdown. A couple hundred healthy volunteer in early Phase I safety studies in patients. And then the more recent Phase II programs in both cardiac surgery and two large studies in general surgery.

I will briefly highlight the features of these Phase II studies. These were parallel studies that were run -- one in the U.S. and one in Europe. All patients were instrumented through PA catheters to look at mixed venous blood. We hemodiluted everybody to a target hemoglobin of 9. And we had protocol-defined physiologic transfusion triggers that were agreed upon up front by the clinicians. This was a drug activity study, so we randomized at the trigger, and then we looked at reversal and duration of that reversal as the endpoint.

In terms of safety findings, the drug was very well tolerated in both studies, in total enrolling about 250 patients. No serious adverse

events attributed to the drug. We had no significant effects on lab values. This included chemistry, hematology and coagulation parameters. And once again, as in Phase I, no evidence of any adverse hemodynamic effects or changes in hemostasis.

This is the platelet data from one of these two studies in Europe that shows the two doses, the blood and the colloid control. You can see at day 2 and day 3 here, we have a slightly lower platelet count drop in the high dose group. But what was important is that all groups have the same acute phase response in terms of platelet count recovery and then stabilization back to baseline. We had no evidence of any enhanced bleeding or other hemostasis problem in these studies.

In terms of efficacy, we were able to demonstrate drug activity based on the reversal of triggers. The primary endpoint in both studies was achieved with statistical significance. That was the delay until triggers appeared once again. We were able to demonstrate oxygenation enhancement, and we now have data to establish hemoglobin equivalency. I will quickly show you the primary comparisons. This is the reversal of triggers. This is the primary comparison of the treatment group versus the blood group that received a unit of ANH blood. We can see

in the two studies where we compare the same dose, we have statistically higher reversal from 70 to almost 100 percent reversal of these triggers compared to blood.

In terms of the duration, once again we had a prolonged duration. Keep in mind, this is ongoing surgical bleeding during the surgical procedure -- a prolongation of the duration. The difference in the absolute magnitude between the U.S. and the European study is due to the different rate of bleeding. In the U.S., we have mainly urologic surgery, and in Europe, we have mainly orthopedic type surgery. Here you can see how the lower dose is approximately equivalent to one unit of blood.

The oxygenation shown here as changes in mixed venous blood parameters. This is mixed venous PO_2 and mixed venous hemoglobin saturation. You can see that the changes are much higher in the oxygen PFC treated patients compared to the blood group.

And then finally, the hemoglobin equivalency. If we look across all three dosing groups in the two studies, we had a very consistent outcome. This is based on contribution of the oxygen delivered to the total oxygen consumption and then comparing that to a standard 50 gram unit of hemoglobin. On average, we can say that a one gram

per kilo dose is equivalent to about 1.5 grams per deciliter change in your hemoglobin level.

One slide on the Phase II cardiac surgery study. This nicely illustrates the concept of an augmented ANH approach. Here we have a control group and a 1.8 gram dose, where we harvested the same amount of blood. And then we have a higher dose group, where we harvested 1.5 liters. You can see that the combination of the higher dose and the increased harvesting, we were able to avoid physiologic triggers during bypass and ending up through discharge with only 17 percent of these subjects receiving allogeneic transfusions, and here is the number of units per subject.

So in terms of our current Phase III clinical development, we have two studies, both focusing on a transfusion indication. The first study is in general surgery. This is non-cardiac surgery patients in Europe. It is a randomized parallel group single blind study design where we are comparing our augmented ANH method against a standard control group where they receive standard red cell transfusion practice. The primary endpoint is reduction and avoidance of allogeneic red cells. We currently have about 28 sites up and running in this study in 7 European countries. We will be adding one

additional country in the next few weeks. This study will enroll a total of 484 subjects.

In the U.S., we have just reached agreement with FDA on a study design for this protocol, and we will be initiating this study shortly. This will be in cardiac surgery in patients on cardiopulmonary bypass, but once again focusing on transfusion outcome. Similar randomized parallel single blind design. Here we are comparing the augmented ANH concept against a control group where we do a routine level of ANA in the controls. The primary endpoint here is avoidance with reduction as a secondary to look at allogeneic red cell transfusion. We anticipate needing about at least 30 active enrolling sites and the number of patients in this study will be 600.

The data from these two studies will then be brought together to support this type of a clinical indication, which would be focused on using the product in conjunction with acute normovolemic hemodilution to reduce or eliminate transfusion of allogeneic blood or preoperatively donated autologous blood in patients undergoing moderate to high blood loss cardiac and non-cardiac surgery.

My last slide I presented in April at a meeting of the Health and Human Services, and it

simply points out how this type of an approach can have a real impact on blood supply in this country. Currently, if we look at the maximum surgical blood order schedule in the U.S., there are approximately 2 million patients that on average consume about 5 million units of red cells in surgical procedures per year. If we look at our augmented ANH technique, and if we assume that we could potentially reduce this requirement from 2.5 by 1.5, then you can potentially across all these surgeries reduce the need for blood by about 3 million units. You can then postulate any kind of a market penetration -- 20 percent, 30 percent or 50 percent. And you can appreciate that anywhere from half a million to 1.5 million units could be spared by this type of an approach. Thank you for your attention.

DR. AEBERSOLD: Any point of clarification type questions?

DR. JOYNER: Mike Joyner, Mayo. You showed in your cardiac surgery trial that you could reduce from around 50 percent to 17 percent with the high dose. But am I correct -- I may have missed something on the slide -- that you harvested 1600 mls as opposed to 1,000. I guess what evidence do you have that you couldn't have taken 1,600 off the first two groups?

DR. KEIPERT: Certainly none from that study. You are absolutely correct. We combined both the higher dose and additional harvesting. Initially it wasn't actually the intent of the study to do that. They were supposed to be harvesting about the same amount to target the same on bypass hematocrit. That high dose group was added later. It was add-on to the study. We initially randomized control in low dose and then we got permission from the FDA to add the higher dose. So it is a very small study, but I think it simply illustrates that the combination of the two appears to work quite well. It is possible that harvesting more blood in the other groups would have further reduced transfusion requirements.

DR. JOYNER: Because correct me if I am wrong, Dr. Weiskopf, but that is only about a third of their blood volume, 1,600.

DR. CARSON: Jeff Carson. Could you -- you demonstrated mean changes in platelet counts, which were in the high 100's or so. Were there any individual patients who had much lower platelet counts? So you presented means. I am just interested in the occasional cases. Were there anybody that got below 50,000?

DR. KEIPERT: I don't believe so. I would have to check. But my recollection is that the

lowest counts were somewhere in the 80,000 range in individual patients. So there is a standard error bar around that mean.

DR. HOLCROFT: Jim Holcroft from University of California in Davis. In your current U.S. trial, will you be using the same degree of hemodilution in your control groups as in your augmented group?

DR. KEIPERT: In the initial -- the initial hemodilution step will be designed to be the same for both groups. And then because we have our product on board, we will then do an additional harvesting step to take the treated group to a lower on bypass hematocrit.

DR. HOLCROFT: I guess my question then would be what about the control group? Are you still going to have equivalent amounts of blood removed for your comparisons?

DR. KEIPERT: No. We will end up with greater amounts of autologous blood in the treatment group. I mean, that is the whole premise behind using the drug. You can take patients to a much lower hemoglobin level than you would normally feel comfortable doing in the absence of an oxygen carrier. Once you have the two groups at different hemoglobins and yet both at equivalent states of

oxygenation or equivalent hemoglobin levels from an effective hemoglobin point of view, then you can take them through surgery and lose less red cells in your treated group. If we carried both groups at identical hemoglobin levels throughout surgery, we have absolutely no way to spare or avoid red cell loss.

DR. HOLCROFT: Well, maybe my question is maybe we can hemodilute patients more than we think we can just using conventional blood volume replacement.

DR. KEIPERT: Well, that is certainly true. And hemodilution has been around for many years. There are a few individuals around the world who are very comfortable and are quite aggressive in their hemodilution. But the majority of clinical sites when you talk to them are just not comfortable hemodiluting aggressively enough to have these types of outcomes.

UNIDENTIFIED PARTICIPANT: Just two points about hemodilution. One, I agree with you. Or three, I guess. People aren't aggressive with hemodilution and certainly that has never been pushed to the limit. The second one, as you correctly point out, there has never been a really well-done, randomized, large, multi-center trial on that. And

the third one is there are tremendous cultural barriers in the operating room to doing hemodilution, as you guys have probably found out, including the fact that operating room time is $15.00 a minute, at least at our place. So you have cultural issues that are preventing these things from happening as well.

DR. KEIPERT: Thank you for that comment.

DR. AEBERSOLD: The next presentation will be given by Dr. William Hoffman of Biopure Corporation. The title is Hemopure clinical update and trauma development program.

DR. HOFFMAN: Good morning. Thanks for inviting us to speak here today. I am Bill Hoffman. I have been with Biopure about a year and a half. I was formerly an investigator for the company at the Cleveland Clinic, where I was director of surgical intensive care. And I have actually given this material to a large number of my own patients.

The material is a polymerized hemoglobin solution. It is a glutaraldehyde polymerized solution. Its major logistic feature is that it is stable for more than two years at room temperature. The room temperature encompasses the range between 2 and 40 degrees Centigrade. The material is bovine derived. It requires no preparation in the sense that it is ready to infuse in the bag. It is low

viscosity. It has a viscosity of 1.3 centipoise. In contrast, blood has a viscosity of around 3 centipoise. And it is isoncotic and isosmotic, so it provides some volume expanding properties as well.

Biopure has, I think, undertaken a rather logical, progressive clinical trial program. It started in the mid-1990's with studies in normal volunteers and included also some studies of patients in non-surgical populations. There were two small studies done in sickle cell anemia and one study done in patients with respiratory failure undergoing ventilator weaning. But the core of the program really has been in the treatment of perioperative anemia.

There have been a total -- and I am just discussing today the completed surgical studies. There have been a total of 9 completed studies. Some of the early ones are outlined here. They included three ANH studies done primarily to assess feasibility in surgical populations that included abdominal aortic aneurysm resection, liver resection patients and orthopedic patients. So right from the beginning of the clinical trial program, Biopure really has not shied away from what could be considered rather high risk surgical patients.

In some of the other feasibility studies

that were done in the U.S. primarily were in radical prosthetectomy patients, gyn patients -- not obstetrical delivery but post-delivery patients who were having tubal ligations -- orthopedic surgery patients. Then there were some large dose escalation studies where patients were treated after an estimated blood loss of 500 mls. In these trials, patients were given single large doses after that blood loss, and the doses ranged up to 244 grams. So this was a relatively large infusion after a relatively small blood loss. In some cases that could be considered a top-loading situation.

There have also been three major surgical studies that have encompassed separate patient populations. The first one to complete was a postoperative cardiopulmonary bypass study. That study included 50 patients randomized to Hemopure and 50 control patients. There was a second study done in abdominal aortic aneurysm reconstruction surgery encompassing a total of 76 patients with a 2:1 randomization scheme, a third as many controls. And finally, we recently completed a non-cardiac surgery study that was done in Europe and South Africa and at all 9 U.S. sites, and that encompassed 80 patients treated with Hemopure and 80 controls.

We have an ongoing Phase II non-cardiac

surgery study which includes stable trauma patients. This is being conducted at three major trauma centers in San Antonio. And we also have an ongoing pivotal study in elective orthopedic surgery patients.

This slide shows the efficacy results for the three major completed clinical trials in major surgical populations. The efficacy here -- the primary endpoint was avoidance or the proportion of patients within the Hemopure group who met the follow-up time point without having received even a single unit of allogeneic red cells. In the post-cardiopulmonary bypass study -- in this study, the maximum dose in the trial was 120 grams or three infusions. The maximum treatment period was only three days. And the efficacy measured at four weeks follow-up was 34 percent. In the abdominal aortic aneurysm trial, which was an intra and post-operative trial, the maximum dose allowed in that trial was just one additional infusion. So we went from 120 grams total to 150 grams, but it had to cover the period of the time during the surgery where there is potentially a large blood loss. The efficacy again measured at four weeks follow-up was 27 percent. And finally in the non-cardiac surgery trial, which encompassed about half orthopedic surgery patients --

this again was done in Europe and South Africa -- here we allowed a maximum of 210 grams and a maximum treatment period of six days. The proportion of patients at the four-week follow-up time point who still had not received a unit of red cells was 43 percent. In all of these trials, patients are not randomized until the decision to transfuse allogeneic red blood cells has been made. So in the control group, all patients received at least one unit of allogeneic red blood cells. The envelope is not opened until that decision is made, and at that point the treatment assignment is defined.

Now one might legitimately ask why these numbers aren't 100 percent. If you run out of dose or if you run out of treatment period or for whatever reason if the investigator wants to give red cells, they are allowed. One of these studies was double blind and these other two were single blind.

This grid here is rather complex, but it just outlines our clinical trial program and the numbers of patients exposed in the various studies by dose. This is the Hemopure group on this side and the comparators for the various studies on this side. You can see that the major surgical studies were all done with red blood cell comparators. Those are the three that I just described. There were a number --

I am sorry, as is listed here, that is not the case. The aortic aneurysm and the post-cardiac surgery study and the non-cardiac study were done with red cell comparators. The studies that were done as dose escalation studies were done with crystalloid comparators. But in total, we have a total of about 421 subjects exposed or treated with Hemopure in completed studies, 298 controls. In our ongoing study, we will have an additional 320 patients treated with Hemopure and 320 controls.

The effects that we have seen in terms of safety variables -- consistently in all of the studies, we have seen transient, mild increases in blood pressure. On average, 10 to 15 mm of mercury in mean arterial pressure around the time of the infusion. This is an effect that lasts about an hour or so after the infusion, and then the patient's blood pressure is generally restored to normal. When we looked at in our cardiac surgery trial what a patient's mean maximum increases in blood pressure were on trial, there were no differences between treatment and control groups.

We see jaundice -- again, in our cardiac surgery trial, this was in 24 percent of the patients. We expect to see that as dose increases. We expect to see an increased frequency of jaundice.

It has been -- and we have looked at this in a variety of different ways in terms of its correlation with clinical events and liver function testing, and it does not seem to be associated with any liver dysfunction. We see transient mild increases in enzymes. This is AST and lipase primarily. Again, these are transient. They tend to last approximately about three days. To date, they have not been associated with any pathologic evidence of liver dysfunction or pancreatitis.

I just want to briefly go over our trauma development program. We are currently doing that Phase II study that includes stable trauma patients. We have undertaken some preclinical work that has included a lethal, traumatic shock model with Dr. Lefer at Temple University, and also an uncontrolled hemorrhage model with some investigators at University of North Carolina. This is a tissue injury model that produces uncontrolled hemorrhage. I will show you some of that data. We have treated one patient, a trauma patient, in compassionate use at University of Maryland Shock Trauma, and we do have the ongoing Phase II study that is including stable trauma patients.

The traumatic shock model is a rat model.

It is a Noble-Collip drum trauma. It produces in controls marked dysfunction of the micro-circulation, severe hypotension, severe endothelial dysfunction. And in this study, Hemopure is being treated after the trauma.

This just briefly is a timeline for the study. The trauma occurs at time zero. The animals are monitored for five hours and Hemopure is given after the trauma is induced.

This slide shows the survival times for five treatment groups in the study. The first group received -- it is sham with essentially no trauma and is given Hemopure at 10 percent blood volume. The survival time for those animals is to the end of the study, 300 minutes. This is trauma plus vehicle at 15 percent volume. Survival time is approximately 100 minutes. Trauma plus Hemopure at 5 percent, Hemopure at 10 percent, and Hemopure at 15 percent. So you can see that in this study, there is a significant increase in survival time, particularly at the dose of Hemopure 10 percent in the animals that received trauma.

Also in this study, endothelial function was assessed. These are the conclusions from the publication. The investigator -- "Treatment with Hemopure exerted significant beneficial effects in

traumatic shock states. It normalized systemic blood pressure and antagonized vascular endothelial dysfunction."

This is a study that is being undertaken at University of North Carolina, two emergency medicine physicians. This is a swine model of profound hemorrhagic shock. Tissue injury is produced with multiple liver lacerations, and the animals are then randomized to receive lactated ringers or Hemopure.

The way the model works is there is a 9-minute injury phase and initial hemorrhage phase. Then the therapy is initiated at 9 minutes. The animals are resuscitated to a mean aortic pressure of 60 by either fluid infusion and the resuscitation is continued until the end of the study, which is two hours.

I am not going to show you all the physiologic data. This is the most revealing. This is the length of survival versus time for the two groups. The control group is the circles and the Hemopure group is the squares. You can see that only one animal in the control group survived. This is an animal that happened to stop bleeding. All the Hemopure animals survived to the end of the study, which was a 130 minute time point.

The conclusions from this study was that there was consistent resuscitation from profound hemorrhagic shock with Hemopure. There was a two-hour survival in the Hemopure group in 100 percent of animals despite a hematocrit of zero for 90 minutes. So there was essentially no circulating red cells. I didn't show you this data, but there was better hemodynamic and metabolic stability after two hours in the Hemopure group as well. Metabolic stability is measured by the usual acid/base parameters.

Our compassionate use patient, just briefly, was a Jehovah's Witness who did accept the material. He was a patient who was in a plane crash. Before treatment, he was in multiple organ failure. He had profound neurologic dysfunction. He was on vasopressors. He had profound thrombocytopenia and was developing ARDS. We treated him four days after his accident and we sustained his life for three weeks, but unfortunately he ultimately died of hyperkalemic arrest because of his underlying renal failure.

I just want to briefly go over the methods in our Phase II trauma trial. These patients are elective, non-emergent surgery. We are approaching trauma from where we have the most data, which is basically the elective surgical population.

So we were going into a highly monitored setting in a situation that we understand best. These will be patients, for example, that have stable, long bone fractures and require surgery 24 to 48 hours after the injury. They are generally going to be ASA-1 to 3. They are randomized at the time of 500 cc estimated blood loss, provided there is an anticipated additional 500 cc of blood loss. We don't want patients in the trial who are going to be resuscitated. So we ask that patients not be enrolled if you anticipate a massive bleed surgery.

This study is single blind. It is randomized. Lactated ringers in equivalent volume is the control. The intent of the study, as Dr. Silverman had mentioned, really is to gain an understanding of transfusion triggers, physiologic variables and some safety issues in this particular population so that the Hemopure can eventually be developed for hospital resuscitation and also for pre-hospital use.

The triggers of the trial are based on estimated blood loss. So the clinical scenario is much like you would treat patients in the field and resuscitate patients in the field. And of course we are looking at safety and efficacy endpoints.

Just to conclude in terms of where

Biopure has been with the product. We have, in completed studies, treated more than 420 humans in 19 clinical trials. The maximum dose we have given is 840 grams. That was a compassionate use patient. In our previous surgical trials, we have demonstrated, given the dose limitations and the limitations of the study, adequate efficacy at the lower doses that were used. To date, our mortality and serious adverse event rates are similar to our control therapies. That is all I have.

DR. COHN: Steve Cohn from Miami. I think we are all concerned about the vasopressor effects of these materials, particularly in the trauma patient where you have uncontrolled hemorrhage potentially. In the DCLHb, the Baxter product, we saw pulmonary hypertension that was pretty severe in pigs, but we didn't see it in people. Have you looked at the effect of your product in patients with pulmonary artery catheters and have you seen any pulmonary hypertension?

DR. HOFFMAN: Well, in our cardiac surgery trial and our aortic aneurysm trial, all the patients have PA catheters. In the cardiac surgery trial -- and Gus has actually published this -- there was a 2 mm of mercury difference between the increase in mean pulmonary artery pressure between treated and

control groups. The one confounding factor is that there was a volume difference. The first dose of Hemopure was 500 ml, whereas the first dose of red blood cells for the control group was one unit, which is approximately 250 ml. And the same is true with the vascular surgery trial. We saw no increase in -- no clinically significant increase in pulmonary artery pressures. We do see about a 2 mm consistent effect.

DR. KRUSKALL: Hemoglobin solutions can interfere with photometric assays of enzymes, liver, pancreas and some drugs. I could ask this question of any of the manufacturers of hemoglobin solutions, but I am getting to you first because actually Biopure has published some of the problems but not the solutions as to how to deal with this. I am wondering how you can interpret to what extent you have organ damage in the setting of problems with the assays and what steps are being taken to work around this?

DR. HOFFMAN: Well, we qualify all the labs -- all of our investigative sites. And our laboratory group has probably qualified 150 labs worldwide. We don't report any laboratory data that is not correct. So all of the interference patterns are well understood. When a laboratory value is

reported, it is the correct value.

DR. KRUSKALL: It may be something that will have to go on off-line or later during our panel discussion. But my understanding of the effects are that they are not necessarily predictable and I would be curious to understand how you correct them and how you know when they are correct.

DR. HOFFMAN: This is a very complicated discussion. But each instrument has different interference -- possible different interference patterns. If something is not predictable, it is not reported. We have to get an alternative assay. But we will not report anything, nor will a hospital report anything when there is a known interference.

DR. AEBERSOLD: That is a good one to come back to this afternoon after lunch. Any other points of clarification? The next speaker then will be Dr. Lou Carmichael of Hemosol, Inc., talking about development status of Hemolink, o-raffinose cross linked human hemoglobin.

DR. CARMICHAEL: I'd like to thank the organizers for allowing us to speak at this meeting. Hemosol has undertaken a development of an HBOC that is safe and effective for perioperative use in surgery to help avoid or reduce exposure to allogeneic blood. This could also help conserve

donor blood for use in other situations.

Let me just briefly describe how this is made. It will be a very brief description. We start with outdated bank blood, blood approved for human use from FDA approved sources. It is brought to our manufacturing facility, extensively washed and lysed, and we go through two viral inactivation steps. First is pasteurization at 62 degrees for 10 hours. I am not showing this slide because somebody stole my new slide -- this is the viral filtration steps. Subsequent to that, the hemoglobin is passed through two column chromatography steps -- anion and cation exchange chromatography to yield hemoglobin that is greater than 99 percent A-zero. We subsequently cross link our material with oxidized raffinose to give us an array of molecular species, about 30 to 40 percent of stabilized 64 kilodalton up to about 512 kilodalton molecular weight. It is then packaged and ready for administration.

We have undertaken numerous preclinical studies, and I would like to just describe two of them to you at this point. The first is the 90 percent exchange transfusion where rats are exchange transfused with Hemolink down to a hematocrit of less than 5 percent. The initial plasma hemoglobins in these animals were around 7 to 8 grams per deciliter.

The rats lived happily ever after or at least until sacrifice at 7 days. What this study clearly demonstrates is that Hemolink is effective in oxygen delivery and that it can sustain life.

The second study was a safety toxicity study in dogs. A similar study has been also done in rats, where total exposures of animals following daily doses for 14 days of Hemolink were up to 5.6 times their total blood volume. Peak plasma levels are shown there. The animals tolerated this procedure well, other than for a small reduction in weight gain. The organ weights were the same in both the treated and control animals. Histologically, all tissues were normal, except for some iron staining pigment that was noted in the liver and in the kidney tubules and tubule cells.

Following this extensive preclinical program, which is actually still going on, we have undertaken our clinical studies. We started off with a Phase I trial in human volunteers followed by two orthopedic and two cardiovascular Phase II trials. The orthopedic trials were of two designs. One was an interoperative autologous donation, IAD. Or as Peter has very nicely outlined to us a few minutes ago, the hemodilution type of approach where blood is harvested and replaced with Hemolink. The other

design was a direct replacement of blood loss with Hemolink after reaching a transfusion trigger during the perioperative period.

Our first trial, of course, was the Phase I study done with escalating doses of Hemolink in human volunteers. This was done at the CRO. These studies showed that Hemolink could be safely administered to humans. There was an effect on blood pressure at doses of about 10 grams and above. There was about a 15 percent increase in mean arterial pressure. There are also transient effects on the GI tract and GU. With respect to the GI tract, at doses greater than 30 grams or 300 mls of product, it resulted in GI discomfort and dysphagia, and there was some urinary hesitancy also reported. And finally, the plasma half-life of this product was found to be between 18 and 20 hours.

Our first Phase II study was an orthopedic trial using the IAD interoperative autologous donation hemodilution, where we removed 500 mls of blood from the patients and replaced it with escalating doses of Hemolink. These patients were hemodynamically stable, that is, the blood pressure and heart rate were easily maintained in the normal range for the anesthetized patients and into the post-operative period. There was no complaints

of GI pain or dysphagia. Rather what we saw was nausea and vomiting, as is typical in post-operative patients receiving narcotics, and there were no serious adverse events reported due to Hemolink.

Our second Hemolink trial in orthopedic surgery, cleverly called Ortho-2, was a multi-center trial again where we were looking at avoidance of red cells using Hemolink as a direct red cell substitute. Once again, the patients were hemodynamically stable. There was no adverse effect that we could tell with respect to renal, liver or pancreatic function as determined by clinical chemistry. And there were no clinical limiting adverse events related to Hemolink.

Let me just go back one. I forgot one point here when I finally got my sheet out. That is why I have my cheat sheets here. In this patient population where we allowed patients to bleed down to a transfusion trigger of 9 grams per deciliter and then would give them Hemolink or the controls would receive red cells, I mentioned we had no GI effects or dysphagia. However, if we allowed these patients to wake up -- or when they woke up from their anesthetic about 8 to 12 hours later, if they reached the transfusion trigger at that point they were given Hemolink and then they saw the same awake symptoms of

discomfort and dysphagia.

We ran two Phase II trials in cardiovascular surgery, both multi-center trials. The one in Canada that was run in Canada and the UK has been completed and the one in the U.S. is just about to come to a conclusion. This study was done in patients undergoing CABG procedure, coronary artery bypass graphing. The design, again, was the interoperative autologous donation, where between 500 and 2,000 mls of blood was harvested, thus being protected from the bypass machinery, the non-epithelialized surfaces. This was replaced with Hemolink in doses up to 1,000 mls.

The objective of this study was to look at transfusion avoidance and to look at oxygenation of patients based on oxygen delivery and oxygen consumption. Also, to look at end-organ function, again with the clinical chemistry parameters.

The study involved 60 patients. 30 were Hemolink patients and 30 were starch patients. In the Canadian trial, the starch was pentaspan, while in the U.S., the starch was hespan.

I have outlined here the most frequently seen adverse events. Nausea occurred, of course, in both populations at about approximately the same rate. The vomiting was probably higher in the

Hemolink group. This is the Canadian study, 203. In the U.S. study, 204, actually the nausea and vomiting values are actually reversed. So I am not quite sure what the significance is yet. As we go into a Phase III trial where we have double blinded, we may get a clearer picture as to whether or not there is an increased incidence of nausea or vomiting in the Hemolink group.

As is expected, there was a yellow-skin discoloration or jaundice seen in about 40 percent of the patients. Of course this was due to the large porphyrin load from the administered Hemolink that needs to be metabolized into bilirubin. There appeared to be a greater increase in blood pressure in these patients -- in the Hemolink patients compared to control, while the decrease in blood pressure was the same -- hypotensive episodes were the same in both groups.

We were very encouraged by the avoidance of transfusion data that we had, although very limited. It is only 30 patients in each group. What we found was that in the Hemolink patients treated with either 750 or 1000 mls in this IAD hemodilution type of approach, that 90 percent of the patients avoided transfusion over the hospital stay, while in the control group it was only between 50 or 60

percent of the patients avoided it.

Based on these studies, we have started a Phase III trial in Canada and the UK and will very shortly start a very similar trial in the U.S.

I just want to spend a couple of moments here talking about the adverse event profiles that we have seen in our patients and the differences that we see in the different states. With respect to the GI system, in the awake patients from the Phase I volunteer study, what we saw was pain and dysphagia. In the surgical population in the post-operative setting, as I mentioned what we see is predominantly nausea and vomiting. This is most likely due to the narcotic analgesics that these patients are receiving for post-op pain and also may be some of the residual effects of the anesthetic agents that have been used. If, however, we give this product, the Hemolink, to patients that are awake 8 to 12 hours after post-op, nausea and vomiting may still be there. But then what we turned to was the awake symptoms of discomfort and dysphagia. And because of that and the other characteristics of the HBOC's, particularly the short half-life, we feel it is more appropriate to use these products or our product interoperatively in an IAD or hemodilution type of approach.

Secondly, with respect to blood pressure,

as I mentioned in the awake patients, there is an increase in blood pressure of about 15 percent mean arterial pressure. In the surgical population, we don't see that. In these type of patients, this is probably due to the vasodilator effects of the anesthetic agent. However, in the post-op period, we do see some increase in blood pressure. However, these tend to be a reduced effect and not occurring in as many patients.

In my last couple of minutes, let me address the issue of risk/benefit for our product as I see it. In the setting of surgery and trauma, there is an inherent morbidity and mortality rate. And when we look at the overall benefits and the risk of these products, what we have to do is keep this in mind along with also the risks of not receiving any blood by patients. We have to include, of course, the intercurrent illness and co-morbidity factors that accompany the disease, and indeed it is a process to try and separate these features from those of the product.

On the risk side, I have listed the side effects and adverse events. The pain and discomfort that patients see as well as the enzyme changes, which may be of unknown significance at this point. It has to then include the serious adverse events

which can lead to morbidity and mortality in patients. I want to point out that at this point, as we approach about 200 patients treated with Hemolink, we have seen no permanent morbidities that have been related to Hemolink.

On the benefits side, I have left out the obvious oxygen-carrying benefit of increased oxygen carriage in the blood and improved delivery through the plasma phase. Rather, I have concentrated on the avoidance of allogeneic blood exposure that Dr. Klein mentioned earlier to reduce the risk even further of the small risk of transmission of disease. There is also the immune modulatory effects where you may expect to see an increased risk of post-op infection. And then you have the reactions to the transfusion itself, the mild or the more severe reactions that can lead to significant morbidity and mortality.

Overall, in our clinical program we have found that Hemolink has been safe and with limited efficacy for use in surgical patients. Thank you very much.

DR. KRUSKALL: I'm very sorry if I missed it, but in your last slide you mentioned enzyme changes of unknown significance. Can you redescribe what those enzymes are and the magnitude of the change and how you are distinguishing them from the

effects of the hemoglobin solution on assay measurements?

DR. CARMICHAEL: I can show some slides perhaps this afternoon to outline some of that. Basically what we see are just transient increases in some of the enzymes. Usually you see a peak at about 24 hours, these resulting over 48 to 72 hours, with no clinical consequence. The people have no symptomatology of disease or adverse event.

DR. KRUSKALL: Can you mention which enzymes these are?

DR. CARMICHAEL: Yes. The liver functions -- AST, ALT, gamma GT, alkaline phosphatase, amylase, lipase. We looked also at creatinine clearance. I can show you that data this afternoon if you want.

DR. AEBERSOLD: The last presentation of this session this morning will be by Dr. Steven Gould of Northfield Laboratories talking about the clinical safety of Polyheme.

DR. GOULD: Thank you. It is a pleasure to be here. Although the title was safety in the abstract we sent in for the panel, actually as we reviewed the questions that were circulated, we felt that the primary focus was on efficacy. So I have changed the make-up of the presentation some. We can

certainly deal with questions as they occur.

Briefly, I would like to go over the key points that distinguish our approach to making a hemoglobin-based oxygen carrier. As with the others, we start with a red cell that can be in-date or out-date. We lyse the cell and we extract the hemoglobin. The important issue for us based on our preclinical evaluation was to eliminate all forms of tetramer, either dissociable or non-dissociable tetramer. We use glutaraldehyde. It is really a two-step process. Human polymerized hemoglobin, which we refer to as Polyheme, consists of first clumping or linking, which is the simple term for polymerization. As shown here, two, three or four tetrameres linked together. The second part of the process, which has been true from the onset with us, is the virtual elimination of all unpolymerized tetramer. So the final release of that is less than 1 percent tetramer in the final preparation.

One unit for us consists of 50 grams of hemoglobin delivered in 500 ml volume at a 10 gram concentration. It was important as a surgically-based team -- we heard about culture in the operating room. Gerry Moss and I felt it was important to have a bag of red fluid that would be similar at least in its oxygen carrying capability to a bag of red cells

to avoid introducing new techniques in the operating room. The P50 is slightly rightward shifted due to the pyridoxyl phosphate and has an intravascular half-life of about one day following infusion. It has a shelf life in excess of one year.

Based on the design and the preclinical studies, we feel that this material represents an ideal rescusitative fluid. It permits simultaneous replacement of the lost volume of hemoglobin that occurs following hemorrhage. As with all the products, it is immediately available due to its universal compatibility. It was important with our interest in trauma from the outset that this material was effective in ambient PO_2.

The last couple of bullets warrant special attention. We heard about the relevance of preclinical models based on some unexpected clinical outcomes this morning. We agree with that. Our preclinical models were vital to understanding what had to be done. Our goal from the outset was to develop a product that would indeed be safe during rapid, massive infusion, since that is how blood is often used in trauma and that is how we anticipate a product like this will be used. We specifically developed a preclinical model that reproduced the vasoconstriction seen in the clinical trials

discussed by Dr. Epstein this morning in the 1970's by Warner Lambert. We tailored our product to eliminate that vasoconstriction. We demonstrated in our preclinical models that the product would indeed support life without red cells, as most of them will do. The issue was safety. So while I won't show all the data, that was key to our progress.

Our current status includes three active trials. I won't summarize the ones that are not in progress. There is a trial in elective surgery at a dose of 6 units. This does involve both ANH hemodilution and interoperative blood replacement. Dr. Holcroft asked a good question. The ANH in this protocol is a 6 unit withdrawal. What is different is that by infusing the hemoglobin, we are able to maintain equal total hemoglobins in the treatment group to the control group. I am shielded from the data. I can't tell you what is happening. But by design, Jim's question was very relevant.

Frankly, what I am going to focus on today is our ongoing trauma study at a dose now of up to 20 units, which represents a two blood volume exchange in patients. This has been a dose escalation protocol that has occurred over the years. Clearly by giving 20 units now, we are dealing with massively injured patients. I am going to share some

data that we did present at the HHS meeting in April that many of you saw. We too are doing compassionate use. I think we have been doing that longer. I am not going to go into detail. Our first 60 or 70 patients have been published in peer review journals and presented at a couple of important surgical meetings.

This is the material I am going to focus on today. This is primarily from the trauma trial. 150 or so patients who have gone through this dose escalation that I have focused on. It was important to us to get to this high dose level. Because we felt, again as stated earlier today, one should be able to mimic the clinical situation in which the product will be used to look for any adverse experiences for unexpected findings. We are particularly gratified by the 53 patients who have received 6 or more units, and the 26 individuals who have received between 10 or 20 units. Again, a one to two blood volume exchange.

Based on the experience and what I will call the successful outcome, we feel we are indeed able to address the important question of clinical benefit in trauma. We agree with Dr. Silverman that the appropriate endpoint is reduction in mortality. The challenge has been how to design a study to

answer that question, and this is how we have approached that.

We wanted to answer the question of whether the use of Polyheme would reduce mortality in trauma in urgent blood loss due to insufficient red cell hemoglobin. That occurs primarily when blood is unavailable. We do not envision some magical property. This is an oxygen carrying solution, and its utility will be in supporting oxygen carrying capability at otherwise unacceptable hemoglobin levels.

A couple of definitions are important. How does one define an inadequate red cell hemoglobin? We and many others in this audience have been interested in the physiology of blood loss for many, many years. We continue to use the guidelines from the NIH consensus conference back in 1988. Everyone here is pretty familiar with this. There is a great debate about how and when to give blood. We simply focused on the range between 7 and 10 as a therapeutically desirable range and let each clinician make their own decision.

Drs. Weiskopf and Joyner and their anesthesiology colleagues have published data suggesting that hemoglobins up to a level of 6 are adequate. Dr. Weiskopf has shown some beautiful data

in healthy, young individuals showing that the compensation in a non-stressed individual to a hemoglobin of 5 is actually adequate. What I believe is universally agreed upon in the literature is that hemoglobins below 3 are life-threatening. In fact, again if one carefully reviews the literature for a published series where blood is not given, usually due to religious objection, there is good support, including some of our own work, that the mortality in a bleeding surgical patient exceeds 80 percent when the red cell hemoglobin drops below 3 grams per deciliter.

With that in mind, we did the following assessment. We used a non-randomized protocol design. This was IRB approved. It involved informed consent from every patient or family member. So it is what might be called a simulated setting, since it was done in the hospital environment where blood was available in what might be called a surrogate population since it included patients who could have received red cells but did not. The analysis that I will review with you includes those who sustained substantial blood loss and did not have initial blood replacement. We are going to look at the high dose group that received 6 or more units of Polyheme as their initial oxygen carrier replacement and compare

mortality to this historical data that I have referred to.

Now how does one do that? Nobody has actually shown this slide. So I want to make sure we all are understanding. On the left there are the normal two components of the blood volume in man. On the right is a representation of a 30 percent hemorrhage, which is sufficient to drop blood pressure showing we lose 30 percent of the plasma and 30 percent of the red cells. Traditional resuscitation involves volume resuscitation and then red cells if and when necessary. On the right is the representation of resuscitation with Polyheme or any hemoglobin-based acellular carrier. We restore the volume and add hemoglobin without giving red cells. So it has the potential to simplify and dramatically change the early care of the injured patient.

From this slide, we can go to the following equation, which explains how we make these determinations. Since there are now two separate hemoglobin carriers, the total is the sum of the hemoglobin carried by the red cell and the hemoglobin carried by the Polyheme. So in essence, the protocol allows patients to bleed and lose red cells, and yet they are not given blood. They are given the Polyheme as an alternative in an effort to maintain a

total hemoglobin in the therapeutically desirable range that we discussed earlier. This is how the determinations are made.

At the end of infusion of Polyheme, a sample is drawn and the plasma and the red cells are separated and one can precisely quantify those two components. Of the 53 patients that had 6 or more units, there were 27 in whom the red cell hemoglobin was below 3 at the end of infusion.

Let's look at an example again just to make sure that everybody follows this. This was a young man who received a high velocity gunshot wound in the abdomen. He arrived in shock in the ER with a total hemoglobin of 5.2 all carried by the red cells. Clearly unacceptable. Consent was obtained from a family member and he was rapidly taken to the OR, where he received on his way and during surgery 10 units of Polyheme in 20 minutes. Two things. First was that his total hemoglobin was increased to 7.5, back in the desirable range. The red cell hemoglobin was virtually indistinguishable. It was all carried by the Polyheme. So it makes the point that we are providing oxygen carrying capacity. The patient subsequently survived.

This is the data for the group. The mean preinfusion hemoglobin using a clinical approach to

transfusion in these rapidly bleeding patients was about 9. Now during the infusion, at the end the mean red cell hemoglobin of 1.8. Clearly none of us that take care of patients would knowingly allow our patients to get to this level. In contrast, the total was maintained in this 7 to 10 therapeutically desirable range. Again, relative to Dr. Holcroft's question, this is the same phenomenon that occurs during ANH, in that you remove unit by unit of red cells and replace it and maintain an adequate total concentration of hemoglobin.

This is really the key slide that I will show you, again that I showed in April at the HHS. This is the mortality data for the 27 individuals. Remembering that the literature would suggest that the mortality should be 80 percent or more. Of the 27 patients, there were 4 deaths, so a mortality rate of 14.8 percent. Now this number is quite consistent as best as one can compare to the mortality rate in major trauma series, which include a variety of injuries. It is very different than a single elective surgical operation. What is more intriguing is of the 27 patients, 20 of them had red cell hemoglobins below 2. There were 3 deaths for a mortality rate of 15 percent. And perhaps most remarkably, there were 5 individuals, including the

example I showed you, in which the red cell hemoglobin was below 1, and none of those people died. We think this is definitive evidence of the ability of Polyheme to successfully load and unload oxygen in this setting.

This slide shows the list of toxicities that were included on the question. Again, I said earlier that we have had a great interest in the hemodynamic changes. I do have data, but in the interest of time I won't project now, showing a lack of vasoconstriction in our volunteers, which is the most sensitive all the way through in our patients. Many of these relate to laboratory findings, as Dr. Alayash discovered. We have not seen any clinical relevance in any of these. Coagulation change is worth a comment. In patients that received 20 units of either red cells or Polyheme who lose 20 units of blood, there are dilutional changes in coagulation that occur. They occur in our patients. The patients do need plasma and a fresh frozen plasma, depending on the circumstances. We have not seen gastrointestinal changes. Before Dr. Kruskall asks me, we too see some of the enzyme elevations. There clearly is interference. I answer the question a little differently, Margot, in saying that for a surgical patient, there is nothing that has occurred

so that on three days when the hemoglobin has cleared we see persistent evidence of laboratory changes. So if something is occurring, it is not an clinically relevant event, which is one of the questions. That has been confirmed by surgeons at more than 20 sites around the country. As Dr. Alayash said, we are not sure how to assess for that. We have not seen it. I apologize for the error in this slide. It should say overwhelming infection, which we have not seen. Everyone of them has had overwhelming injection, but that is due to the protocol.

So in summary, again we agree that mortality is the appropriate endpoint, and we think this data, although small -- a small part of our total sample -- is meaningful in documenting a reduction in the mortality of otherwise lethal hemoglobins. It occurs by maintaining an adequate total hemoglobin. This was how this product was developed. That is how it is being used, and the data, that I will be glad to expand upon, does document that it is safe during this rapid, massive infusions. Thank you.

DR. WEISKOPF: Weiskopf, San Franciso. First, Steve, thank you very much for your kind comment. I want to -- a point of clarification. I want to make sure that I understood what you said and

did not misunderstand it. That is with respect to the trauma study and the mortality data that you showed, do you have a -- is there a control group that has received blood, or is this strictly just patients given your product without a -- then the control is strictly historical?

DR. GOULD: The patients I showed you here was a non-randomized, single group study. We have published data in a trauma series, small, 44 patients, showing now difference. Our largest randomized trial is our elective surgery trial, and as I say I am shielded to the data, although there is not a difference in mortality. We are not sure how to design a control group to actually do that, and we think this is the most appropriate way to do that.

DR. RABINOVICI: Reuven Rabinovici, New Haven. Can you elaborate, Steve, a little bit about the inclusion and exclusion criteria in your studies?

DR. GOULD: Sure. For the urgent trial, essentially any trauma patient. The patient has to be an adult, 18 years or older. They have to -- what is written is that they can get in the study if their systolic blood pressure is under 100. That is really not the most common entry point. The most common is a clinical judgment on the part of the surgeon that urgent transfusion is likely to be needed. So

basically what happens, Reuven, is that the patients come in and are evaluated and go to the OR and pretty much the patients are consented whenever possible. We lose patients in whom consent cannot be obtained. So the decision is made either on the way or early in some instances, and in the operating room in other circumstances when it is necessary. The attempt is to potentially enroll all patients that are on their way to the OR following trauma.

UNIDENTIFIED PARTICIPANT: In these people with very low red blood cell hemoglobins that you have successfully taken through surgery and got them to the ICU and so forth, what happens to their both red blood cell hemoglobin over the next several days or week in the unit and the Polyheme hemoglobin?

DR. GOULD: Well, as you would anticipate when I told you it has an intravascular half-life of about a day, that means there is a full life of about three days. So there are numerous simultaneously moving targets. If a patient receives 10 units and goes on to lose another 30 units of blood before the surgeons control the liver or the vena cava, half-life is measured in terms of minutes for either Polyheme or red cells. All the surgeons are nodding their heads. They know what we are talking about. If the operation is over and we take a stable patient

who is loaded up with Polyheme, there is a predictable decay over the next three days, following which if their red cell hemoglobin is that low, those patients will need some red cells. So that is one of the lessons that is being learned and one of our goals in going to these high dose infusions was to truly get experience and learn how to guide that therapy. This is not a total replacement for blood by any means as we have heard. It has a number of benefits that haven't really been put on the table here yet related to its use in this urgent setting. Even if blood might be available. I'll leave that until later. So we had a focused question, but the direct answer is if the red cell hemoglobin is low enough that in three days they will not have regenerated their own red cells, they will need some red cells. Absolutely. Which again is why we think looking at mortality, as Toby has said, is an appropriate way to look at this.

DR. VLAHAKES: Gus Vlahakes, Boston. In these large dose interoperative studies, how is your protocol structured with respect to component therapy for ongoing bleeding, let's say, from a big liver injury? What have you told your investigators with respect to that? And the second question is when you analyze safety and tolerability in these massive

replacement studies -- and this question really will go to the other vendors who were involved in trauma studies -- if you are administering such a product with ongoing bleeding, particularly if the bleeding is massive, and you have given 20, 30 or 40 units, can you really say that there is tolerability of 40 units of product if it is coming out in the form of bleeding? So how do you analyze what dose has really been retained from the standpoint of analyzing safety data?

DR. GOULD: Yes. Those are both good questions. Let me start with the last one just to finish up. That is a very important question. You can only deal with the patients. Patients getting 20 units are going to be massively bleeding patients. So buried within this are patients who have received that total dose and retained the bulk of that dose. You can't read things into the data that is not there.

With regard to coagulation, the longer version of what I said about dilution is important. Number one, as with the approach to giving an oxygen carrier, be it red cells or Polyheme, in the trauma setting we can't mandate. I mean, everyone here will agree that every patient in every setting is different. So they should do whatever they do. If

they have a protocol, they should use a protocol. If they have Margot running their blood blank, they will do it one way. If they have somebody else, it will be another way. The one difference is the following. When patients lose 10 units of red cells, and we all teach the same things about you shouldn't need anything and they may need platelets first, those patients are getting packed red cells today. You have to remember that packed red cells include a small amount of residual plasma. So by the time one has given 10 units of packed red cells, depending on how many -- if you said 50 cc of residual plasma in each unit of red cells, a 10 unit red cell recipient may have received 500 ml of plasma. A patient getting 10 units of Polyheme has 10 units of hemoglobin. So what we have alerted the trauma folks to is that they have got to pay attention that they may in fact need some of these things earlier. It is simple dilution. If you go to 30 or 40 units, everything is washed out. The platelets should be the same. There are no viable platelets really in stored blood either. That is how we have approached that. But we have not tried to say how they should do the replacement in the OR because that will vary from surgeon to surgeon, site to site.

DR. AEBERSOLD: We have finished on time.

I think all the speakers for that. There is an hour and a half for lunch, from now to 1:30. So let's be all back here. There is no reason not to be back here promptly at 1:30. We will start right away at 1:30. Thanks.

(Whereupon, at 11:54 a.m., the meeting was recessed for lunch, to reconvene this same day at 1:31 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:31 p.m.

DR. AEBERSOLD: It's probably 1:30, even by the slowest watch. A quick administrative announcement. A pin was found and it says Scotland on it. It is a sword. It was out on the table there. So if anybody is missing that, it is here. If it is still here, we will put it back on the table later on.

What we thought we would do for the question and answers period is, as you can see, have the speakers from the manufacturers session sit up here so they all have a microphone and are available handily to answer the questions. This means that the questioners will need to come up to either this microphone here or the one on the other end. Either one, depending upon which is closer to you, I suppose. I have been asked by the transcriptionist that each person introduce himself or herself before they ask the question. Which reminds me that I don't think I introduced myself. I am Paul Aebersold from the FDA, Office of Blood, Division of Hematology.

The agenda has it panel discussion and questions addressed to manufacturers. We are going to open this up to the entire workshop. If there get to be so many questions that the panel members don't

have a chance to get their questions in, then we will maybe try to cut back and have some sort of priority. But let's just open it up completely for the time being and see how it goes. We have an hour. We have this morning's presentations -- I believe there was one question right at the end that was addressed -- Dr. Carmichael, did you have -- I think we need to push your button on each microphone when you want to speak.

DR. CARMICHAEL: Could I have the first slide up there, please? I was asked about some of the clinical chemistry changes that take place. I promise I will be brief. I just bought this, so I want to make sure I get a chance to use it.

This one addresses the issue of renal function and looking at creatinine clearance. This was from our Phase II cardiac trial and looking at creatinine clearance and serum creatinine. What you can see is that the two points, the baseline creatinine clearance and then at six hours and then again at three days. Post-pump what we found is that both the Hemolink treated and the starch treated patients went down and by three days they were back up to control levels. And then just confirming that with the serum creatinine levels that really weren't different at any of the time points through the study

period. I think the conclusion here is that renal function isn't really affected by these products.

What we are looking at here is our panel of liver enzymes -- AST, ALT and gamma GT on the bottom. We are looking at baseline at post-op day 1, 2, 3, and post-op day 5, which is generally the day of discharge. AST, what you see is there is a similar rise in both the Hemolink and the starch treated patients that come back down to control values. With ALT, there really just wasn't any change and the same with gamma GT. It stayed down within the control range.

Can I have the final slide, please? We can come back and talk to these in a minute. The question was asked earlier about PA pressures. And what we have here is the PA pressures in the cardiac trial -- again Swan-Ganz catheters. And starting at the 250 ml dose, 500 ml, and 750 dose -- I don't have the 1,000 dose here. But what you can see is that there is really no difference in the PA pressures between the control and treated arms starting at induction -- sorry, just post-induction when the swan went in, and then post-bypass one hour in ICU, 6 hours, and 24 hours, when the catheters came out. So I think it is clearly evident here that this product has no effect upon PA pressure, similar to what was

said earlier for -- I guess it was you, Bill, that mentioned that. Thank you very much for the slides.

DR. AEBERSOLD: If we could have the lights? Thanks. Open for questions.

DR. WEISKOPF: Weiskopf, San Francisco. I would like to ask a two-part question to all of the panelists -- well, perhaps only to those in the hemoglobin-based products. I am not sure this applies to the perfluorocarbon-based, but if does certainly Dr. Keipert ought to feel free to chime in as well. It relates to searching for toxicity. There are two issues I would like to ask. One has to do with pancreatic and the other myocardial. First, the pancreatic, I think virtually all of the hemoglobin-based products have seen increases in circulating pancreatic enzymes post-administration. And I would like to ask those who have conducted studies what they have done to look for whether or not this represents pancreatic pathology. Whether there has been any follow-up in those patients in any way to carefully examine for pancreatic pathology, or whether one has merely followed blood enzyme levels.

The second relates to myocardial toxicity. I know -- I think we are all aware that some of the preclinical studies some years ago indicated the potential for myocardial toxicity of

hemoglobin-based products. Mike, I was a little surprised to see that you indicated that in one of the Baxter studies that there were some issues with respect to myocardial ischemia. So I would like to know from those that presented what the various sponsors have done looking for myocardial ischemia and in fact what the findings have been.

DR. SAUNDERS: I guess since I was the first speaker, I should respond first. Certainly, we did see elevation of enzymes -- of the pancreatic enzymes in the clinical studies, both with the recombinant hemoglobin as well as with DCLHb. Our experience with the recombinant hemoglobin was smaller doses and many fewer patients. We never saw an episode of clinical pancreatitis that we could relate to the product. There was clearly other explanations. On the other hand, with DCLHb and the breadth of experience and the higher doses that were administered, there were episodes of clinical pancreatitis demonstrated. So that is one.

What did we do to evaluate those during clinical trials? We had -- both Baxter and Somatogen had contingencies built into their protocols so that there were imaging studies done if there was a persistent elevation of the enzymes to a qualified level -- two or three or four times the upper limit

of normal of amylase and lipase.

As far as the myocardial toxicity is concerned, yes I did indicate that we had seen in that unusual, unexpected serious adverse event category an imbalance in myocardial ischemia. You have to recognize that this was a huge data base across multiple studies and multiple indications, and those episodes of myocardial ischemia were not all from the cardiac surgery study. They were in peri-op and elsewhere -- orthopedic surgery. I don't know necessarily what to make out of those episodes of myocardial ischemia. I don't know that they represent a specific episode or an indication of toxicity. We evaluated those clinically, certainly with the recombinant hemoglobin clinical development plan. In cardiopulmonary bypass surgery, we had very intensive monitoring going on. That is one of the advantages of doing studies in that setting. It is normal practice. And we followed with transesophageal echo as well. Unfortunately, in -- there was no regular routine or actually much of any success in obtaining post-mortem examinations in any of the patients who died in any of the trials. So I can't really comment from a histologic/pathologic standpoint.

DR. HOFFMAN: All patients in our trials are followed clinically. So it is not simply a

matter of just following the enzymes. Patients have a physical exam every day, for example, and are followed clinically. Presumably a case of pancreatitis would come up as an adverse event or a serious adverse event in the trial.

In our ongoing pivotal study, it is built into the protocol that any patient who has a serial elevation of lipase on two consecutive days will have an imaging study and see a GI consultant. So we have some built-in prospective monitoring of our patients in the pivotal trial.

With regard to myocardial toxicity or myocardial infarction or ischemia, patients in all of the studies have had serial enzymes and have had serial EKGs, and that is true of our pivotal study as well. I don't have the data in front of me. I can't tell you what the rates are, but they are around 1 percent, I think, is what we have seen, which is what is typical for the types of surgical populations that we have been in.

DR. CARMICHAEL: Let me go back and say a couple of things about the pancreas amylase/lipase. When we started the cardiac trial, we saw some elevations in both amylase and lipase, and I went back to the anesthesiologists and the surgeons and said what happens in your usual patients. A couple

of the older guys said,"oh, we used to measure this all the time and we saw elevations in amylase so we stopped measuring it because nobody was sick". Just to comment on what Bill said, these patients are being seen on a daily basis. We have transitory elevations in amylase and occasionally lipase. It peaks at 24 hours and is back down by 48 or certainly by 72 hours. We too had a protocol instilled where if the patient's amylase and lipase were elevated greater than 48 hours, a gastroenterologist was called and the patient would then get a CAT scan and go forward. We have had two CAT scans on two patients, and they were normal. In one case, we ended up with a serious adverse event because we made the patient stay in the hospital for two extra days to get the CAT scan. So it is hard to say. We just have not seen clinical signs and symptoms of any disease -- any pancreatic disease in our patients.

I guess the other thing to add is just an anecdote and it is only one patient and only one investigator, but he got a report of an elevated amylase on his desk a day or two after surgery, and he went running upstairs to the patient to say,"my God, this patient has got pancreatitis", just in time to sit down and have lunch with the patient. The patient was not sick.

With respect to cardiac toxicity, we have not seen that. In the cardiac trial we follow, of course, CKMB serially throughout it, and there is just no difference between the Hemolink treated and the starch controls.

DR. GOULD: I actually want to clarify a little of your comment there, because we have not seen increases in amylase, short of trauma patients who have had pancreatic, biliary or intestinal injuries. We looked for it. We have the same cautionary steps built into the protocol. In the event amylase reaches a certain level, there is an imaging protocol we embark on, and we have not had to do that on a single patient yet.

In our elective surgery trial, while we are shielded, I do see all the SAEs that come in, and there has been nothing there. That is probably our best data looking for myocardial ischemia, and we have not seen any difference either. Now while some may say how come you are not seeing it, since we haven't seen it and we haven't worked with it in the laboratory, I have no personal experience. My concept is based on the time course of the amylase elevation that has been described and the alleged lack of clinical pancreatitis, I view it as a smooth muscle spasm phenomenon. There are surgical models of

producing hyper-amylasemia or pancreatitis in that fashion. So, again -- and I may be wrong because I haven't worked with it -- I think it is an NO mediated end that may or may not be dose related that results in a sphincteric contraction resulting in a spike in amylase, which I would not expect to necessarily produce symptoms in an anesthetized patient. There were reports early on in a number of trials in healthy human volunteers having abdominal pain, nausea and vomiting, again with a fairly rapid resolution. So that is my concept of why it is happening and why we are not seeing it.

DR. AEBERSOLD: We are being transcribed.

UNIDENTIFIED PARTICIPANT: Is everybody following prospectively cardiac enzymes or only in those patients in whom one becomes clinically suspicious of an event?

DR. SAUNDERS: Prospectively.

DR. HOFFMAN: Same here. Prospectively.

DR. VLAHAKES: For those who have observed cardiac enzyme elevations, as you look over the patient populations studied, do you have the sense that there is any increased susceptibility, for example, related to age? In other words, is there something about the observed cases to suggest that it might be occurring in patients where there may be

subclinical previously undiagnosed coronary disease?

DR. SAUNDERS: Well, my response is unfortunately we didn't really look -- when we terminated the DCLHb program, we didn't go back and do an integrated summary of safety, which in a sense might have been something that would have been ideal to be able to answer that very important question and a very interesting question. My suspicion is just from looking through the serious adverse event reports and the case records that there probably is some significant component of underlying, maybe relatively silent beforehand coronary artery disease in elderly patients coming to orthopedic surgery for instance.

DR. VLAHAKES: Okay. For Dr. Keipert, what is the persistence time of the product and how is it disposed of physiologically?

DR. KEIPERT: By persistence you are talking about intervascular retention?

DR. VLAHAKES: Correct.

DR. KEIPERT: The blood half-life is very dose dependent. It ranges in our healthy volunteer top-loading studies anywhere from 6 to 12 hours at a 1.2 or 1.8 gram per kilo dose. Currently we are using 2.7 grams per kilo in surgical patients in Phase III. It is ultimately disposed of from the

body initially by phagocytic uptake by macrophages and Kupffer's cells in the liver. And then the fluorocarbon molecules leave the body much like an anesthetic gas. They are solubilized and carried in blood lipids and blown off through the lung.

DR. VLAHAKES: Okay. And in your interoperative protocol, what were the transfusion decision criteria for readministration of autologous blood? How was that -- what were they?

DR. KEIPERT: In the Phase II studies that I very briefly summarized, we had a list of physiologic transfusion triggers that were generated by consensus with a group of about 40 anesthesiologists and surgeons, and we used both absolute values and changes from baseline related to hypotension, drops in blood pressure, or blood pressures below 60, tachycardia, a certain percent increase, or an absolute of 100 or 110 depending on whether it was the European or the U.S. study. We had PVO_2 values below 38, and then we had changes or significant increases in cardiac output and any evidence of myocardial ischemia by ECG. And then we also built in a hemoglobin floor of 6. So those were kind of the battery of triggers that we were working from.

DR. VLAHAKES: Okay. And for the

investigators working in hemoglobin who are designing clinical studies in trauma, I would be interested in the vendors' philosophies about study design with respect to control groups. How do you control a trauma trial for an HBOC solution?

DR. GOULD: The selection of a control group for any study is dependent on the question that is being asked. If one wants to address mortality reduction, as suggested by Dr. Silverman and as agreed upon by ourselves, I think you have a dilemma. I can't speak for Mike here, but their approach, as I understand it and as presented today, was to begin with a very high mortality group receiving conventional therapy including blood and see if the infusion of a new product, in this case their hemoglobin, could reduce mortality. That was laid out very clearly. The hypothesis was clear. The statistics were clear. The outcome was clear also. We all covered a lot of material quickly. We do not feel that there is any magical, lifesaving benefit to our polymerized hemoglobin. It is an oxygen carrier that is capable of providing hemoglobin, and we have therefore focused our trauma trials, as I set up, in a life-threatening red cell hemoglobin level, and for that purpose would qualify when blood is unavailable. That may immediately take you down a path of what is

an appropriate control group. Scientifically, it would be a group of patients sustaining trauma and being resuscitated without red cells. But we can't do that ethically in an environment in which blood exists. So because of the ability to separate the red cells from the plasma and make those determinations, we did this in a non-randomized trial this time. And we think the data answers the question -- the data that I have presented -- as to whether the infusion of Polyheme in that setting of life-threatening red cell hemoglobins will reduce mortality. And all I can do is go to the literature and find what is there. There are probably six series that I consider really reasonable -- large size series published with sufficient documentation of hemoglobin and mortality outcome for me to say that the mortality is very high, whether you say 80 percent or 70 percent or 90 percent. It is a high number. And I can compare that.

The alternative is to go to an environment where blood is truly not available and actually do your study, and that gets into a number of other logistic issues and safety issues. So for us, based on the question we are asking, the patients were their own controls based on the ability to make these measurements. If you are transfusing red

cells, you cannot distinguish the transfused red cells from the patient's endogenous circulating red cells. So that is how we designed the study with the selection of the control based on the question we were asking and the endpoint we wanted to achieve, which was a reduction in mortality.

DR. SAUNDERS: I guess I need to say that this is really a very complicated question, and one that I am not sure that we really have the answer to. I can only reflect on the experience, particularly with the U.S. trauma trial and the European trauma trial with DCLHb. And that is that what we chose to do was to use DCLHb as the add-on therapy to maximal standard of care therapy that would be used in a trauma patient situation. So the control is truly those patients who receive everything else but DCLHb. I would agree that it is an awfully high bar to try and get over. But at the time, that was the wisdom of the approach to dealing with trauma. It was to be able to show a significant difference. How would you select the controls in the future? I mean, we are wrestling with that question now. I think one thing that we have clearly learned is that it does require very careful selection of patients as well as very careful, clear and well-regulated procedures standardized through the protocol for all of the

decisions that are made through the course of that patient's hospitalization. And with that kind of long-winded answer, I would also invite Dr. Ed Sloan, who is somewhere here and who was the principle investigator in the U.S. trauma trial to make comment if he would like to as well. If he has any comments beyond what I have already said. Ed, sorry to put you on the spot, but I know this is one of your favorite subjects.

DR. SLOAN: Thank you. The only comment I would make about the choice of mortality as an endpoint and the need for a control is that without the ability to have concurrent controls, it will be very difficult to know whether or not mortality has actually been reduced. A number of trauma trials -- there have been head trauma, our DCLHb study -- we have been surprised because the control groups performed exceptionally well in studies. So historical controls probably are inadequate for answering the question of does a product reduce mortality.

DR. SAUNDERS: And I would just add to that my own presentation -- reiterate the presentation from this morning and to give specific numbers to what Dr. Sloan has already said. And that is that we predicted, based upon historical controls,

that this patient population should have a 40 percent mortality rate. We found a 17 percent mortality rate. I would say that is highly significant.

DR. SLOAN: Some of the issues that you encounter, especially with historical controls, is the fact that it is hard to know in multiple trauma, especially when you are examining different disease states -- blunt versus penetrating trauma, vascular trauma versus solid organ injury trauma -- it is hard to know without a concurrent control whether or not the groups are comparable that you are comparing. And even when you have concurrent controls, it is quite difficult to know whether or not your prediction of what you expect the mortality to be is going to be equal across groups. When we looked at our own DCLHb data and you look at what TRIS would predict as far as outcome, you can see that those models are based on data -- even if the data is only 3 to 4 years old, it is hard to know whether or not that data can be generalized to a subgroup that we look at in real time. So I think without a concurrent control, the question is difficult to answer at best.

DR. HOFFMAN: This is a rather naive perspective of someone who has not designed a Phase III trial study. But I think I agree with Ed that a

concurrent randomized control group is essential for evaluating mortality. And the setting in which the effect is likely to be the largest of an oxygenating fluid is field use or in other settings where blood is not available. So that would be the goal of Biopure, I believe, to learn enough and understand enough so that that sort of trial could be designed.

DR. AEBERSOLD: Any other comments from the manufacturers? I have a message for Dr. Carolyn Sidor to come to the reception desk or the registration desk outside. The choice of control population is a difficult one and Baxter was looking to a very critically ill population. I think the obvious point is if you talk all-comers in trauma who need a transfusion, you wouldn't be looking at a 40 percent mortality rate but a lower mortality rate, and that would be a much larger trial. So it has an effect that way.

We have a patiently waiting question here.

DR. FIOLO: I am Mario Fiolo from Texas Tech University. I would like you to address the question of vasoconstriction. There is no question that animal experimentation has shown very significant vasoconstriction responsible for an increase in mean aortic pressure and dropping cardiac

output. That has been well documented. Dr. Hoffman, a report from Cologne, Germany, Kuster et al., a paper in Cardiovascular Anesthesia published in 1996, in which Hemopure was used and randomized with ethyl starch for hemodilution in patients undergoing aortic surgery. Where Hemopure was used at a dose of 3 ml per kilogram -- so they were not massive doses -- the effects were an increase in mean aortic pressure of 40 percent, an increase in calculated systemic vascular systems of 70 percent, and a drop of cardiac output of 25 percent. So I wish you would comment on that.

Dr. Gould, do you think that -- you have made a point that you eliminate all tetrameres from your solution. Do you think that the tetrameres are responsible for vasoconstriction? Like if we push that point a little further, with regard to trauma, we have known after World War II that victims of crash injury that develop renal failure, that was due to myoglobinemia and myoglobinuria, although myoglobin is only a unimer. Could we expand that concept that a tetramer may be responsible for toxicity, and therefore if we eliminate all tetrameres from the hemoglobin solutions, we would have eliminated an important factor of toxicity?

DR. HOFFMAN: The paper you are referring

to is one of the ANH studies that was done in Germany around 1994. What was published was serial hemodynamics over a fairly extensive time period that included the post-operative period in patients who received ANH with Hemopure versus ANH with hetastarch. And at one time point which was not prospectively defined, they did find an modest decrease in cardiac index and an increase in mean arterial pressure. But it was only at that one time point. If you subject it to a more conventional analysis, it would not have been significant. But having said that or even given that, at that time the cardiac index was actually going up. Between the time previous and the time after that, the change was actually increasing and the patient's metabolic parameters were improving in the sense that the base deficit was less in the Hemopure treated group than it was in the hetastarch treated group at that time.

DR. FIORO: I think we are talking about a different report. In this particular one -- and I gave you the reference -- not only was cardiac output decreased by 25 percent, but when they calculated oxygen delivery and oxygen consumption, they were significantly decreased. And the conclusion of those two papers were -- these were from the Department of Anesthesiology, University of Cologne -- the

conclusion was that this hemoglobin solution actually reduced oxygen delivery and oxygen consumption. And I would suspect this is due to vasoconstriction. This is my original question of how that was addressed.

With regard to the Baxter clinical trial, the question -- obviously Dr. Hess here who performed the animal experiments with a similar product and found just that -- a significant sustaining vascular resistance -- a pulmonary vascular resistance increase and a drop in cardiac output. So the question would be, that work by Dr. Hess would have not indicated that perhaps this alpha alpha hemoglobin had excessive vasodynamic effects.

DR. HOFFMAN: There were two papers published from the same study. One was published in 1996 and I believe one was published in 1998 or 1999. They came out of the same experiment, though. And the conclusion was that delivery did decrease at that time point because the cardiac index decreased and that is a major component of delivery. But consumption was unchanged. And furthermore, as I said, they were both going up at that time point. The investigator isolated one time point and analyzed that point out of many. Overall, there was no difference in that study between the hetastarch group and the Hemopure group. It was a relatively low

dose. And the conclusion of the study was that it appeared at this does that Hemopure offered no advantage over hetastarch in this ANH on hemodynamics in this setting. But it wasn't that it was detrimental on oxygen delivery.

DR. GOULD: Dr. Fiolo, the answer to your question is yes. We believe that the small molecular weight species is responsible for the vasoconstriction. And again that is primarily based on our sensitive awake primate model that we used to empirically arrive at our current specification for tetrameres. So the answer is yes.

UNIDENTIFIED PARTICIPANT: My question is to Dr. Gould. I would like to congratulate Northfield for their ongoing efforts in trauma. Certainly you are in the forefront of investigating the role of anti-oxygen carrying fluid in patients with post-traumatic hypertension. It seems to me that what you have for now is a result of one -- I would say the first -- prospective studies that directly compared any blood substitute with the standard of care in which you were able to show that your product, Polyheme, can sustain life. It can do that with minimal side effects and can also reduce the need for allogeneic blood transfusion. However, the study was severely criticized, primarily because of the small

number of patients -- I believe 44 total. And also for the fact that it did not include any efficacy criteria such as morbidity and mortality.

On the other hand, you have some favorable results also from Phase II clinical trials, in which you have demonstrated some beneficial effect on mortality. However, in this study you don't have any control groups. And the question that I have for you is what is your game plan or what is your strategy based on the information that you have in hand, especially because it seems that you advocate the use of mortality as an endpoint, which as you know takes a lot of time and a significant number of patients to show differences?

DR. GOULD: That is a good question. And at this point in time, I can only say we are impressed with these results or gratified with these results and we are reviewing them in detail to decide just how to proceed. I can't give you a specific answer at this moment.

DR. KRUSKALL: Margot Kruskall from Boston. I wanted to just follow-up on the study design and then ask one other question. It seems to me that the importance of a control arm has been emphasized here, but I also think that it is important to look at the patients who were excluded -

- who don't even get in to being considered for either the control arm or the experimental arm. Since it strikes me as conceivable that you may have excluded patients who are extremely sick, for whom one might have been able to put a substitute to a challenge. Or conversely, you might have picked extremely sick patients to consider in your trial, and that would also be helpful to know. So I would be interested in hearing from each of the manufacturers what proportion of patients were excluded in your trials or did you make any attempt to even consider those in analyzing your results?

DR. SAUNDERS: Well, certainly screened patients versus actual enrolled patients is significantly different. I am not sure how I can begin other than we were sort of -- we were talking about the trauma trial. So I will use that as an example. As I have mentioned in my presentation, there was a bimodal distribution of the patients. We actually saw a very high proportion of patients who were very, very severely injured, to the point where mortality was almost a certainty. And this was counterbalanced by a group of patients who were very mildly injured, to the point where mortality wasn't really an anticipated outcome at all. That creates a real problem because the real group that you want are

the ones in the valley in-between. Those are the ones who potentially have a high potential for mortality, yet they are -- to be able to really see a difference with the treatment. To be able to really punctuate a difference.

But getting to your point about those people who were excluded, there were patients who did not -- who were in the intent to treat group but did not actually receive product. And this was one of the difficult analyses that when we went back and looked at the results as well, because the majority of the control patients died in that situation and a smaller proportion of the DCLHb patients died. So that is one of the clues that there could have been some impact on randomization bias that had the investigator somehow been able to perceive what the treatment was that the patient was going to be given, and they didn't want to go through all of the rigors of the trial and said if you are not getting the good stuff, then we will just do what we normally do.

DR. KRUSKALL: Actually, your answer I think helps me to crystalize my question. But then I won't pursue it with the others unless somebody has a comment. I think in terms of efficacy, I understand your interest in seeking the middle ground of patients between your bimodal distribution. But in

terms of safety, though, I think it is important to have a much broader enrollment or at least consideration because in fact you stress your product substantially more when you use patients who are extremely ill or who have very small chances of survival, and it may be an opportunity perhaps to see things you don't want to see about your substitute that perhaps were missing when we look at a finely honed population of patients for efficacy trials.

My other question is to each of you in turn, and I will sit down to hear the answers. You each have a different outdate on your component, and in each case we haven't heard the rationale for the outdate. I am curious as to what it is that outdates in your product and also what happens as the product nears its outdate in terms of changes in its safety profile.

DR. GOULD: The outdating is a function of primarily the product being maintained within the release specs. You have certain release specifications as you do with a unit of blood. And at certain points in time, if the material goes out of those specs, it is no longer approvable. It also is a function of where you are in your development how much validation you have. So some of the stated times may in fact be longer than they currently are.

To some extent it is an evolving target.

DR. AEBERSOLD: Any other responses to that question?

DR. HOFFMAN: I would give a similar response. I am going to ask Maria to respond on behalf of Biopure.

DR. AEBERSOLD: I think part of the question is that the spec may be a long way from what you are manufacturing at. So that you could be drifting toward your specs over time.

DR. HOFFMAN: While she is coming down, I would like to talk about the inclusion criteria for our trials. The earlier studies were highly selective in terms of having very specific inclusion/exclusion criteria down to what the platelet count had to be, et cetera. For our ongoing orthopedic trial, the patients are ASA 3 or less. That is the rather objective but rather inclusive inclusion criteria.

DR. GAWRYL: Maria Gawryl, Biopure Corporation. We look at all of our final product specifications, especially methemoglobin and molecular weight distribution. We have data out now to 7 years, and we don't see a change in those parameters. We also look at other stability indicating assays that include protein denaturation, hem release, and by reverse phase just looking to see

what happens to the protein.

DR. SAUNDERS: Only one additional comment and that is that we look at similar types of things, looking at specifications that change when the product outdates. I have no data and I am not even sure how we would necessarily always go about systematically being able to differentiate adverse event profiles of new product versus older product that is still within the time frame or within the expiration time. To be able to do that kind of fine-tune differentiation of the product would be a bit difficult.

DR. CARMICHAEL: I'll just add one more thing. We do things similar to the other companies. We of course do ongoing testing. With our frozen product, it is frozen at minus 70, that is probably good indefinitely or certainly for a number of years. And we run checks at periodic times just to make sure the product has not deteriorated or is not modified in any fashion.

I need to go back and respond to one other thing. Someone asked about the removal of the 64 kilodalton or the tetramer from the product. We have looked at that extensively in preclinical studies and with respect to all the parameters that we have looked at, it does not appear to make any

difference whether you have 64 kilodalton material in your product, and we have 30 to 40 percent of it, or not. Blood pressure changes are the same, et cetera, all of the things we have looked at. Thank you.

DR. KEIPERT: In terms of the fluorocarbon emulsions, we are primarily monitoring the physical properties of the emulsion, the largest determinant of that being the median particle size, diameter over time. And that was actually one of the reasons why we reformulated back in 1993 was to obtain a pharmaceutically more stable product that doesn't change as much over time, where the product that we now have after a year in storage appears to be identical to the product that we previously had produced fresh. So if you speculate what might happen when the product is near its expiration date, if the particle size was slightly larger, we might expect a higher incidence of fevers, let's say, in a conscious volunteer, because that incidence rate decreased on us when we went from the larger particle size emulsion to the smaller particle size emulsion.

DR. KRUSKALL: Your answer was more in line with what I was hoping to hear from everyone else. I was interested in the rationale for the specifications. But maybe I will just pick on Steve as an example. Do you know that at the end of your

shelf life of the component that the extent of the tetramer appearance hasn't changed from the time you first created the component?

DR. GOULD: Margot, in fairness, I think some of us are being a little hesitant. Some of that is proprietary. So generically, I tried to address the issue that within the confines of those release specs, there may be changes. Although, again, I say that the outer limit may not be clear as we do these ongoing studies. I am not trying to avoid the question, but it is what is appropriate for the audience.

DR. GUNARTI: Anil Gunarti from (inaudible) Chicago. My question is basically for hemoglobin group and trauma trials. Hemoglobin, we now know that once it is outside the red blood cells, it is a very active molecule and is not only vascularly active, but on various other smooth muscles also. And obviously if a substance is that active, there are lots of interaction with other circulating substances as well as drugs or substances which have been consumed by patients. So in a trauma trial, we don't know, for example, an alcoholic intoxicated person might come with an accident and alcohol is also metabolized through the liver and hemoglobin is also. So my question is concerning all

these complications and non-epinephrine drip blood substitutes and hemoglobin interactions, were some inclusion/exclusion designed to take care of these problems or are they necessary? Or if they are not necessary, then the reasons for that. Just some light on that aspect.

DR. SAUNDERS: Well, that is also a somewhat complicated but an excellent question. There is a bit of a double-edged sword with putting in too many inclusion/exclusion criteria, because then you narrow your population to the point that it is not really generalizable to the group that you want to potentially prescribe it to. That is one aspect.

In our particular trials, the decision was made to try to open it up as much as possible to be as generalizable as possible, and to not confine the investigators to the point where it may make it even more difficult or impossible to perform. There are some -- with that said, I think that that may have also been a bit of the undoing of the U.S. trauma trial as well. Had there been very sharp, crisp criteria, we might not have had the difficulty of the bimodal distribution of the population. It may have been more of an even distribution across relative risk groups. So it is a somewhat

complicated view of how do you decide which is -- which do you want to add and which do you want to delete?

As far as concomitant illnesses or concomitant medications, I can only tell you that for the relatively small patient components that we had in the U.S. and European trauma trials, we looked at everything. We tried to find any correlation that we could to explain the imbalance in the mortality and we were unable to find that key if there was one.

DR. COHN: Steve Cohn from Miami. I first want to compliment you as representatives of industry in a field which the burden of proof is getting harder and harder to demonstrate now that blood is getting safer and safer while you are trying to develop your products. But I am going to ask you some what I think are reasonably difficult questions. Because I think that you are doing equivalency studies, whether it be mortality or adverse effects, in the setting where you are most likely to show equivalency. In other words or let's say safety. You take orthopedic hip as one multi-center trial that is going on, and you look at people who are likely to require 1 to 2 units of blood. Not redo orthopedic surgery or redo cardiac surgery or trauma patients who come in inextremis. Most of the trauma

patients in Dr. Gould's study could sign consent or had a surrogate. So, therefore, we may be eliminating in some ways the group that we are most likely to use this blood substitute in. So we were talking at lunch about the main concern of all of us is off-label use of this. So, i.e., the prehospital setting. And this is the area where we don't have blood available. We already have a safe product available if somebody is in the operating room. You can give them two units of blood.

Pre-hospital setting or in the emergency rooms at centers where there isn't a big blood bank and in the operating room, where we are massively transfusing a liver transplant patient or someone with a big hole in their liver. So I guess the question I have for you is how generalizable -- as you just said, how generalizable is the data that we are getting on either safety or efficacy on trials that are done with two units equivalent. You know, you are selecting a population that doesn't require a lot of blood on average. I realize that it is a control population. Or let's take it another step. The augmented ANH. How generalizable is that to me, the user. Because when the FDA says this is safe, I can tell you at our center we are going to use it instead of lactated ringers. That is where we are

going to use it. We are going to use in the field on our helicopter in patients in shock. So we are going to use a lot of it. Is the safety data going to be generalizable? Thank you.

DR. SAUNDERS: I guess this is sort of saying how close to real life can we get without actually getting there. I mean, it is an extremely difficult task for the design of the clinical trials to be able to define what are the limits and how can you best provide a broad population. And the only answer that I can really give is when you get into Phase III trials, you do large numbers. You are going to see a distribution of those patients that hopefully does more accurately reflect what is a broad population, so that the end user has some idea and that the labeling really is meaningful for being able to give direction to a prescriber.

DR. GOULD: Steve, let me answer a little differently. I think the patient who is going to need 12 to 20 units of blood is a sick patient. We don't have all 20-year-old trauma patients. As you know, the spectrum of age in the trauma population is changing. We have a number of octogenarians that have been treated. Many people in their 50's and 60's who come in. As I said this morning, there virtually are not exclusions other than getting

consent. So we are going to see people with coronary artery disease and with COPD and with some intrinsic renal disease. So in our case, we have felt from the start, just as you said, we need to be prepared for all uses of the product. That pushing the dose -- we are sort of coming at it from the other end. Since we can't control it on the inside, if we go to the high dose, it is the sickest patients that are going to get those. And it is hard for me to believe that an elderly patient who can get 10 or 20 units and tolerate it, that a younger population getting 1 or 2 units is not going to tolerate it as well. So that is how we have come at this.

DR. HOFFMAN: I just want to clarify a few things on our orthopedic trial. Most primary hips don't get transfused anymore. So these are basically patients who have substantial blood losses -- redo hips, spines, and it includes elderly patients with fractures that are well into their 80's and 90's. There is no upper age limit on the trial. The only trial constraint is that they be evaluated as ASA 3 or less prior to enrollment, and that they consent obviously.

I don't think that the data is necessarily generalizable to the example that you gave. In these patient populations, you do get into

situations where occasionally there is a surgical mishap and there has to be a resuscitation is going on and the patient is on trial. We get someone enrolled with tight aortic stenosis, and normally if you had known that, you would have made that patient ASA 4. You get a patient with severe 3 vessel disease enrolled and you didn't know that before. All that happens. We are going to have limited information in these selected patient populations, but we will have that information. If you were to come to me and say I want to use it in the helicopter, I would say, no, we are not going to sell you any. This is our label. It is an elective orthopedic surgery patient population ASA 3 or less. So we would have to do additional trials for these additional indications that you imagine the material might be used in in the future.

DR. CARMICHAEL: I think we would have to say also that I am sure none of us are limiting our patient populations to any extent. The orthopedic population of patients are getting up to 70 and 80 years of age. And in the cardiac surgery programs, you are looking at all ASA 3 patients here. So we are looking at relatively sick individuals that we are covering through this surgery. One other aspect that comes to this is that there are differences with the

different regulatory agencies also. We have one regulatory agency that limits the patient population and we have another regulatory agency that says turn it open to everyone. And I agree with the latter. I think what we have to do is bring in -- if we are doing cardiac surgery, we cannot eliminate the sick patients. We need to include those in our trials.

DR. KEIPERT: Let me just make one comment about the augmented ANH concept. This is really designed for use interoperatively in primarily elective surgery patients. It is a blood conservation strategy where you a priori know that this is a surgical procedure where you would expect with a fairly high likelihood that the patient will need maybe 1 to 4 units. If it is a case where you are already anticipating needing 15 to 20 units, it is probably not going to have such a big impact. I think I agree with the other speakers who said that we can't do trials to cover every potential clinical indication that people can dream up for these products. So in our discussions with regulatory authorities, we have picked a clinical indication that represents a broad use of the product. In our case, we are doing both a large pivotal study in non-cardiac surgery, and that includes a variety of non-cardiac procedures, and we will have a U.S. trial in

cardiac surgery. Some of the other indications may get tested later in Phase IV type situations, and maybe there will be labels on the product that says this drug has not been evaluated in trauma patients or others, but that is the best we can do right now.

DR. AEBERSOLD: A well-timed question and it will be coming back tomorrow in the surgery discussion and maybe today as well. We have a couple more questions here. Let me just say that this business of extrapolating, it is I think on the questions that were distributed ahead of time. It is almost a philosophical discussion as to whether people will pay any attention to the exact labeling in the patient population. And FDA and I think everybody would be concerned if one relatively low risk population were studied and the product were used widely in a much higher risk population.

DR. HOLCROFT: Holcroft from Sacramento. In the interest of time, I won't give any background to my question. But how much information is available for using any of these products in patients with head injuries? I have reasons for asking, but I won't bore you with them.

DR. CARMICHAEL: I have none.

DR. HOFFMAN: We have no clinical data for head injury.

DR. SAUNDERS: The only data that we had in patients was in the U.S. trauma trial, and that was actually one of the sources of imbalance that was related to a bad outcome. There is preclinical data, but I am not even sure I could comment on that.

DR. AEBERSOLD: I believe isolated head injury was excluded in that trial.

DR. SAUNDERS: It was to be excluded in the trauma trials, but the point was that we did actually have some patients who were admitted. This is one of the difficulties of dealing with very severely injured patients. One of the other issues is that sometimes it is very difficult to immediately assess the patient and determine when you need to make that quick determination of are we going to put this patient in the trial or not and then do they or do they not have a significant closed head injury.

DR. GOULD: There is not a lot primarily because of consent issues.

DR. KEIPERT: And we have no data because we have always done elective surgery.

DR. CARSON: Jeff Carson, New Brunswick. I commented on this earlier this morning that much of the data that was presented with adverse effects were means, and means can be very misleading. What is going to get you guys into trouble is those

occasional patients that have extreme effects, i.e., thrombocytopenia of 20,000 or blood pressures that go up to 50 mm of mercury or higher. So the means are largely not helpful. So my first question is is there any -- what is the experience in those giving hemoglobin substitutes with extreme blood pressures. How high have these pressures gone up in patients exposed to these drugs?

DR. HOFFMAN: We did a specific analysis of every patient's maximum pressure in all of our trials, and we found no difference between treatment and control groups. So when you compare everybody's peak pressure from baseline or peak increase from baseline, treated and control, there have been non-significant differences. I don't recall a patient who has had thrombocytopenia to that level. That was not a specific issue that we had.

DR. SAUNDERS: For reach of the individual trials, we do look at the extremes, particularly if it is associated with an adverse event. Just a generalized comment, that is one of the reasons that we went back and did sort of the unexpected, unusual serious adverse event evaluation was to look at those outliers to try and find out if there were patients at the extreme as far as safety considerations. It did obviously have a bearing on

the decision to terminate the program last year.

DR. CARMICHAEL: We did a non-surgical trial in renal failure patients on dialysis looking at another issue. But people would report the adverse event of an elevated blood pressure when they received Hemolink. And then when you go back and look at the record -- it was a crossover study, so we had them in other dialysis periods -- the pressures were not different between the treated and the control patients.

DR. CARSON: So having a good control group can also save you is what you are saying, of course.

DR. SAUNDERS: But I guess I would comment that we certainly did see a pretty consistent rise in blood pressure associated with DCLHb and with Optro for that matter.

DR. CARSON: Were there any extremes?

DR. SAUNDERS: I don't recall any episodes. There were patients who did require anti-hypertensive therapy. The elevation in blood pressure was transient and no clinical consequences thinking back on all of the adverse events -- the serious adverse events. I don't recall any clinical consequence to elevated blood pressure. Specifically no one blew a vessel.

DR. HOFFMAN: Just generically, we all, I am sure, look at shifts from normal to high and from normal to markedly abnormal. So looking at extremes is a routine part of analyzing data from these clinical trials.

DR. NESS: Ness, Baltimore. One of the -- on the laundry list of toxicities, one of the ones that potentially seems to me to be most worrisome, particularly if this use expands to relatively healthy elective surgery patients, is that of bacterial sepsis, and yet I haven't heard anything from any of you about events of bacterial sepsis in any of your clinical trials, although the animal data to some extent is somewhat persuasive. Have you not seen it or is this something we don't have to worry about?

DR. SAUNDERS: I guess I kind of blew by it pretty quickly. In the unexpected serious adverse event analysis that I did, sepsis was one of those that did not show a significant difference between DCLHb and the control group, and neither did it with Optro. So that was one of the ones that maybe -- from preclinical data, yes, you would maybe expect there should be something that we would see, but we did not clinically.

DR. JOYNER: Joyner, Mayo. I guess I am

a little confused as I think about things. We started with Dr. Klein today explaining to us how the blood supply has become safer and so forth, and as I listen to you folks talk about the designs of your trials. It seems to me that they fall into two categories. One set of trials is designed to show that you can have a product that would be useful in the absence of red cells if you were in a hostile environment or if you were in some place where red cells weren't available. It could be used to temporize patients until they could get definitive transfusion therapy and surgical therapy.

The other trial is the ANH trials, which seem to me are strictly designed to use less blood. So has essentially the goal of industry now been shifted from trying to replace blood with a safer product -- has it shifted from trying to replace blood with a safer product to just try to use less blood? And then if the answer to that is yes -- the second part of that loaded question is if the answer is yes, then with the safety of the blood supply as good as it is, maybe 1 in 50,000 fatal problem associated with a transfusion, aren't you going to have to do a bazillion patients to prove that your compound is good or as good as blood?

DR. KEIPERT: I think your last comment

probably answered the question. We certainly are not prepared to do a bazillion patients. I think the goal is really just as you stated, to look at transfusion to reduce allogeneic exposure in patients and ideally to have some significant subset of those patients avoid allogeneic blood completely. Because then you have a truly meaningful "benefit" to that patient. The risks of blood, the known risks -- and there are some unknown risks -- are hard to calculate or hard to numerically put probabilities on. So to actually design a trial where you would go against those kind of numbers would be almost technically impossible to do. And I think that is why FDA has agreed that reduction and avoidance of allogenic blood, although a surrogate by definition, does impart and imply clinical benefit to the patient.

DR. JOYNER: I guess an implied benefit. But if we are talking about the very rare and unusual potentially catastrophic complications that might only be seen in one in a thousand or one in ten thousand patients, I guess that is what would concern me. It is that the product is fine and you can reduce the use of allogenic blood, but you have rare, unusual complications that just aren't going to be picked up in "reasonably" small, even though I am sure they seem very large to you, clinically trials.

I don't mean to be nihilistic or skeptical here, but I think what you are trying to do is really hard.

DR. AEBERSOLD: The FDA agrees with this that it is very hard, and I think it is one of the questions to be discussed, that is, what kind of assurance do you want that this product is no less safe than blood. That as a surrogate endpoint, we recognize at the FDA that it would take tens of thousands of patients to really measure the adverse events of a blood transfusion in a control group. Do we want -- and yet if you had that size trial, who would conduct it? And so then you start talking about a statistical matter of what level of assurance are you willing to accept really as an uncertainty as a limit. If you can't detect one in a thousand events in a clinical trial, are you willing to accept that as a product as a doctor?

DR. JOYNER: Well, then it would depend on the magnitude of the events and the level of the catastrophe associated with it. I think about -- if you look at problems people have with blood transfusions, many of them are not immediate -- like hepatitis B -- and if they are going to kill somebody, they are going to kill them a long ways off in the future. And I think about people having hips replaced or knees replaced, older individuals with

co-existing disease, and if a small fraction of those people who typically do pretty well known ended up having some sort of catastrophic bad outcome and if you knew about it, it would really kind of bias you against using that particular alternative to transfusions. So my bias is blood is awfully safe. So, I mean, I hate to be even meaner to you guys, but you've got to -- boy, the crossbar is awful high.

DR. SAUNDERS: You know, I have to -- I really appreciate the fact that you have noted the challenge for us. What I think we also need to recognize is that there are many other facets of giving blood that are beyond what Dr. Klein presented this morning. I mean, it is not just HIV and hepatitis. But there are a number of other issues associated with blood as it progressively ages. There is diminished oxygen delivery because of the depletion of 2,3DPG. There are concerns about immune suppression. There are a host of things that we just don't even know yet. So I think to a large extent, we don't even know what all of the risks are or what the risks may be in the future of blood. I am not so sure that I agree with you that blood is imminently safe. A question might be -- an interesting and provocative question -- if we were talking about blood today rather than blood substitutes, how would

you feel about potentially approving such a product?

DR. JOYNER: One of the most common operations requiring transfusion is cardiac surgery, and I think the data shows that in the best centers, the mortality from first time CABGs is between 1 and 2 percent. So we are talking 1 in 100. I don't know what it is on valves and redos, but it is substantially higher than that. So we are talking about something that is -- whether it is blood or maybe even your products -- that are several orders of magnitude safer than the procedures that the individuals are going to have.

DR. KEIPERT: One other comment, and certainly we all agree that blood is safer than it has been in years past, but I think one of the other issues is to keep in mind the patient's perception of that risk, which is probably several orders of magnitude higher than the current mathematically calculated risk of some of these adverse events. So it becomes almost a patient-driven therapy. If they know there is an alternative, they will want to use it and they will want it. So that is also something that needs to be factored in here, even if it is just a one or two unit reduction for that patient.

DR. GOULD: I think what you are -- I

want to qualify your comment a little bit, Mike, because I think you are really talking about elective surgery. I mean, I think that is what you were intending when you talked about ANH. There are -- you know, I mentioned this morning that we might get a chance on the panel to talk about -- even when blood is available in urgent settings -- if you think about it, everybody on the panel comes from a big hospital. How many times do you have more than one bleeding patient at once? For Paul and Margot, the problems in the blood bank can become significant in terms of quantity and in terms of quality assurance and in terms of wastage. So there are -- I don't want your comment to be taken out of context. I agree with what you said, but I think the concept of safety and alternatives in elective surgery is different than in trauma. Even if blood is available in the urgent setting, there are a number of significant logistic benefits. At the FDA, we have talked about this. You may not quite have the mechanisms to deal with those other benefits, but they are real in urgent settings, even if blood is available.

DR. JOYNER: The possibility that you might be able to give somebody 10 or 20 units of a product and then put the clamp on and then switch

over is kind of using it in place of O negative. It is conceptually attractive, but it clearly deserves scrutiny.

DR. GOULD: Again, that is why we have pursued this high dose. To be able to walk down that path.

DR. AEBERSOLD: We will take one -- oh.

DR. HOFFMAN: I was just going to -- our safety endpoint in our trial is a comparison between the safety profile of patients who received treatment with blood primarily and patients who received treatment with our product primarily. It is a comparative analysis. It may be that one group is superior to another in safety, but I wouldn't necessarily assume it was the red cell group. There may be safety issues related to blood that are not known, and that may predispose patients to significant morbidity, along the lines of what you were saying.

DR. JOYNER: I couldn't agree with you more. The only problem is the signal and noise ratio. It is that many of the bad complications of blood are long term and take a long time to show up. So you wouldn't see it in a 28-day or 6 month or even a 6-year trial some of them. And then the other problem is that the frequency is so low. Say you do

500 patients and what if the frequency of a particular adverse event is one in 5,000. You might not pick it up.

DR. HOFFMAN: Let me just give you an example that illustrates what I am talking about. It is not necessarily a real physiologic example. But let's say we find at the end of the study that 30 percent of the patients in the red cell group had DVTs and say another 5 percent of those develop pulmonary emboli and the rate was substantially reduced in the group that received Hemopure. That would mean that we had learned something new about patients who are treated primarily with blood that affects the primary morbidity in orthopedic surgery patients. And otherwise let's say the safety profile was similar. How would you react to that as a physician?

DR. JOYNER: That would be helpful, and I would do two things. One is I would do some quality assurance with the nursing staff to make sure the patients were moving more and didn't get DVTs. I mean, that is a little bit of an unrealistic example, but I see what you are saying. So if you had some other complication that was less, that would be interesting, yes.

DR. AEBERSOLD: Let's take one last

question for this session, hopefully a quick one.

DR. YAR: Thank you. Jonathan Yar, University of California at Davis. I would like to congratulate Dr. Hoffman on his comments, because I think we are missing the boat a little bit. We are not looking at mortality. We should be looking at morbidity from blood transfusions. There may be an enormous amount of morbidity that we accept as standard of care currently that we may not have to accept that. I don't know that for sure, but it is only by double blind randomized studies that we can actually find that out.

DR. AEBERSOLD: Okay. We'll move to the next session for a while, until 4:00, I guess is our scheduled break. Dr. Barbara Alving from NIH will chair or moderate the next session, I guess. And we will move the panel members up to the front.

(Whereupon, at 2:49 p.m. off the record until 2:50 p.m.)

DR. ALVING: And you can see that we have our work cut out for us. Our questions have been preordained, which is usually the case when the Government invites you to be on a panel.

I hope we have some latitude in the answers. Is that true, Dr. Silverman? Before we begin, I would like to have each of the panelists

introduce himself or herself and tell just a little bit about your own personal interest in this area. Let's start with Dr. Vlahakes.

DR. VLAHAKES: My name is Gus Vlahakes. I am a cardiac surgeon on the staff of Mass General Hospital, Boston. I have worked in this area from primarily the research standpoint from 1986 and have been a PI on a cardiac surgery trial with the Biopure product.

DR. JOYNER: My name is Mike Joyner. I am an anesthesiologist at the Mayo Clinic in Rochester, Minnesota. I am interested in this because my main intellectual interest in life is oxygen transport in humans, and blood and its use in surgery is a key element in that.

DR. COHN: My name is Steve Cohn. I run Trauma Critical Care at the University of Miami, and I am particularly interested in this because I like to exercise and I get very hypoxic. Actually, I have been involved in both preclinical trials as well as clinical Phase II trials with the Baxter product when it existed, and I have been involved in some way with some of the other products. I am particularly interested as I feel that there is a great need for an alternative to blood in situations where blood doesn't exist in the trauma situation.

DR. NESS: My name is Paul Ness. I am a hematologist and I am Director of Transfusion Medicine at Johns Hopkins. In addition, I am the Senior Medical Director of the Red Cross region that serves this area, Baltimore and Washington. I have been interested in alternatives to transfusion for a long time in terms of things like autologous blood, hemodilution, and I have been involved in a couple of the trials of the Northfield product at Hopkins.

DR. RABINOVICI: I am Reuven Rabinovici. I am the Chief of Trauma in the Surgical Critical Care at Yale University. I have an ongoing collaboration with the Navy on the development of liposome encapsulated hemoglobin, which unfortunately is not being discussed today.

DR. CARSON: I am Jeff Carson. I am Chief of General Internal Medicine at the Robert Wood Johnson Medical School. I am an epidemiologist from a research perspective and have been interested in the last 10 to 15 years in the relationship between anemia and outcome mortality and morbidity and interested in transfusion triggers. That has been my main focus of research.

DR. KRUSKALL: I am Margot Kruskall. I am the Director of the Division of Laboratory and Transfusion Medicine at Beth Israel Deaconess and

Harvard Medical School. And I have been interested in blood conservation in general, autologous transfusion and blood substitutes in particular, ever since involvement in the early Fluosol trials in Jehovah's Witnesses. I continue to be interested in the debate about how to measure efficacy and safety.

DR. WEISKOPF: Richard Weiskopf from the Department of Anesthesia and the Cardiovascular Research Institute at the University of California, San Francisco. I guess I have been involved with artificial oxygen carriers in one way or another for more than 20 years. My research interests have to do with examining oxygen transport in humans and trying to develop a definition where one can have objective measures for the need for transfusion of red cells or artificial oxygen carriers.

DR. HOLCROFT: My name is Jim Holcroft. I am a vascular and trauma surgeon at the University of California in Davis. I have no personal experience at all with any of these products, but I have to concede a bias that I would like very much for one of them to work or maybe several to work, if for no other reason than for combat casualty care and for care of other individuals who are injured in places where blood is not available.

DR. ALVING: Thank you. So we have a very

distinguished panel. In addition, there are many distinguished members of the audience present who have had great experience in some way or another with blood substitutes. So we may have to call upon you also for your advice. But now we have got to get down to business. We have the first question in the trauma section. This is under Section 2. Safety will be interspersed, I think, with some of our discussion. But the first question is should mortality be the endpoint of choice for clinical trials in hemorrhagic shock or exsanguinating hemorrhage? Are there any endpoints that would be good surrogates for mortality? So first of all, let's discuss mortality. Dr. Vlahakes?

DR. VLAHAKES: We'll start at this end. The short answer that I would give is yes. And the reason being is that the potential for this group of patients -- this group of patients has the potential to be very heterogeneous. Also heterogeneous in monitoring and preinfusion data that you are going to have available, except for the relatively well-defined and probably small number of parameters that are reasonable to gather in a very fast moving clinical scenario. Mortality is also an unambiguous endpoint. And particularly with the kinds of things that we have seen in clinical trials today, that is

probably going to be your most reliable single indicator of efficacy.

DR. ALVING: Does anyone have any views other than that or would like to enlarge on that?

DR. COHN: I would just like to say that I think that while it may be unambiguous, it could be somewhat misleading if you had -- if you relied on total mortality. By that what I am saying is that as two-thirds of the patients who actually arrive alive to the hospital die from their head injury, and that would be, let's say, unlikely to be the result of the lack of a transfusion or let's say some safety adverse effect, let's say, related to the blood substitute. I think that what we would like to do is get non-head injury related mortality or at least a priori say that we will look at that subset separately as the head injuries may not be affected in the same way, or they may well be affected in a different way.

DR. ALVING: Dr. Carson?

DR. CARSON: The main reason that you think about surrogate outcomes is because you have trouble powering studies to look at the outcomes you care most about. In a trauma setting where there is very high mortalities, your sample size calculations will be reasonably favorable because you will have

plenty of outcomes. Therefore, I don't think the surrogate outcomes are going to be as necessary in this situation. Like others have said, it is pretty unambiguous, feet up or feet down, and it is pretty hard to argue about it. So I think this is a setting in which mortality should be able to be powered at a reasonable number. So I would pursue that as an outcome.

DR. ALVING: Richard?

DR. RABINOVICI: I think that the answer is yes. The ultimate outcome measurement for trauma patients is survival, and we should stick to that. And the problem obviously is the number of patients that are required to come to any statistically significant conclusion and the time that it takes. Having said that, I believe that we should resort to some surrogate endpoints, and there are a very limited number of endpoints that are validated vis-a-vis outcome. I think probably the most prominent one is a serum lactate measurement. There were several studies, both experimental, by Joan Seigal, and clinical by Tom Scalia and Jean-Luis Vincent from Brussels which demonstrated that the measurement of serum lactate is probably the most accurate predictor of outcome. It has been shown that patients that were able to clear their serum lactate levels within

24 hours had nearly 100 percent survival rate, which dropped to approximately 15 percent after 48 hours. So I think that as an endpoint of resuscitation which correlate with outcome, this is probably the number one surrogate endpoint that I would advocate. It goes with the base axis, which correlates very well with serum lactate determination but was never shown, unlike the serum lactate measurement, in prospective studies. But it correlates very well and in many institutions it is used in parallel or rather than serum lactate.

The other endpoint that is evolving, I believe, is the gastric mucosal pH determination. There are several recent studies primarily by Raoul Rabatori from Virginia which show pretty good correlation with outcome that is with mortality, and I think this should be considered as well.

I would like also to make a point that many of the oxygen-related endpoints have never been shown to correlate with mortality, that is, oxygen delivery, oxygen consumption, and other parameters. The relationship between oxygen delivery and oxygen consumption have never been shown really to predict outcome. I know that most people did monitor these endpoints in their studies, but eventually they may be not the surrogate point of choice.

DR. WEISKOPF: I am going to differ with my distinguished colleagues and offer the opinion that I don't think that mortality is in fact a good endpoint. It is a very insensitive measure in that one can have a therapeutic major impact, either positive or negative, without affecting end mortality, especially in a group that has a high expected mortality to begin with.

In addition, one might have -- whether you want to call it unfortunate or fortunate -- distribution of patients in a group that has such a wide variety of pathology, for example such as occurred in the Baxter study, where even though randomization has occurred, because of the wide heterogeneity of the sample of patient population that one could have by chance in fact a better group in the therapeutic, or as Baxter happened to have, a worse group in the therapeutic arm, and have a chance of showing a change in mortality that may or may not have anything in fact to do with the therapeutic. So I don't believe that mortality is in fact a good or reasonable measure. One ought to have a more sensitive measure that one can rely upon rather than mortality.

DR. HOLCROFT: Why not? I think mortality should be used. The other surrogate endpoint that I

would consider, though, if mortality rates were equivalent would be neurologic outcome. Because I think that makes a difference to the patients. So if indeed a treatment could give a survivor better neurologic function, then I would use the product. I wouldn't accept anything else. I wouldn't accept lactates or gastric mucosal or pH or whatnot. I don't think it is going to help to tell the family that their daughter died, but she cleared her lactate. It is just -- I don't think that matters. And if indeed these really are good measures -- if the serum lactate or whatnot really is a good measure of survival, then you should be able to show it with your product. You should be able to show that their survival is better. There are ways to deal with confounding co-variables, and we have experts on this panel who would know far more about that than I. You can eliminate some of the variability introduced by pre-existing illness or by the characteristics of the injury.

I would make one last comment. I am not going to keep it a secret. Why I think the head injury part is so important. I can see Dr. Cohn's point, which is kind of, well, the head injury deaths are preordained. Therefore, if you enter those patients into the trial, then they will dilute out

any beneficial effects that you might have with an experimental agent. That may be true and I don't know for sure. However, my belief is that not all deaths or neurologic disability resulting from head injuries are preordained. I think there are patients who could benefit in terms of their neurologic function and in terms of their survival if indeed you could resuscitate them early on. Specifically I am referring to in the field. I think almost everybody agrees that hypoxemia and hypotension, and especially the combination in a trauma patient, kills you. And if it doesn't kill you, it will leave you with a severe neurologic disability. So some of these agents, by increasing the oxygen carrying capacity of the blood, in a situation in which there is no other alternative -- I am referring to pre-hospital care -- I think some of these agents potentially could save lives in patients with head injuries.

DR. ALVING: We are not going to let Dr. Weiskopf off the hot seat. He doesn't like mortality, so he has to give us some alternatives.

DR. WEISKOPF: Okay, fair enough. But let me perhaps give one more sentence of explanation why I don't like mortality. And that is based on the assumption that the only thing that is affecting mortality is oxygen delivery in these patients.

After all, these compounds are -- their prime modus operandi is delivery of oxygen. You and I, Jim, both know that these patients die of many other things other than just oxygen delivery. That is why I say it is an insensitive measure of what the proposed therapeutic effect of these compounds are going to do. So I would look at measures that are looking at oxygen transport in whatever -- oxygen delivery and oxygenation of tissues -- in whatever population we are studying, whether it is trauma patients, elective orthopedic patients, cardiovascular patients. I don't think it matters. I think the issues are the same and that mortality is not an issue unless of course the compound for whichever sponsor is producing it is in fact having some lethal effect, which I don't think any of us believe that that is the case here. But you certainly don't want to be increasing mortality. But I don't think it is a reasonable measure, because that is not what this compound is -- that is not the primary function of this compound.

DR. KRUSKALL: So I want to put another blow in against the argument of abandoning mortality. I think we can design the study so that they can take into account a lot of these confounding variables. And whether we like it or not, we are now

stuck with the results of the Baxter trial that suggests in fact that as coarse as mortality may be as a measurement, there is a problem and that it is one that may be correlated with a higher incidence of serious adverse events. I think we have to start with mortality, and only after we find equivalency can we then also factor in these other more sensitive measures. I think we would be omitting a very important outcome if we didn't include it.

DR. RABINOVICI: Jim, I agree with you that the clearance of lactate in a young girl who died wouldn't matter for the family, but I think nothing would matter to that family, including how much packed red cells you gave the patient. I think that the problem is that the large number of patients and the huge investment which is required to achieve statistical significance as far as mortality is concerned, which is an ultimate endpoint. So we are trying to sit here whether surrogate endpoints would still do the job. In that respect, I think we have to be very selective and very careful in what endpoints or which endpoints we are using. And I think we should resort to the literature and to what is available. I think it is essential that any surrogate endpoint to be selected will correlate with outcome. And those that I have mentioned are the

only ones available so far. If you have a better one, I would be glad to hear that.

DR. VLAHAKES: The mortality endpoint is a very interesting one, and in a certain sense it is integrative. Because inherent in it is also a safety implication. In other words, if the use of one of these materials in the trauma setting results in restoration of oxygen delivery but produced a significant increase in potential septic complications, that is still an important parameter that enters into the ultimate efficacy of it. So the mortality parameter I think is useful because it covers both sets of information and a lot of very useful information will come out of such a trial.

DR. COHN: I don't think anyone is suggesting using mortality as the only endpoint. I think that we always say in the trauma area that there is no one who is less expensive and has a lower incidence of complications than the person who dies immediately. We don't have to worry about vent days in that patient. I think that you can certainly add in base deficit, lactates and some of these other things which I think are important. I don't think PHI is important. We just did a prospective randomized trial showing now benefit of measurement of intramucosal acidosis in terms of our management.

But that aside, it is an essential endpoint. And as Dr. Kruskall said, we just had a trial that showed a mortality difference. I think we have to start and at least show minimum that whatever trial is done doesn't have a mortality difference. I do think we should do a planned subset analysis, excluding or including the head injury population, which I think is different.

DR. ALVING: Yes?

DR. CARSON: I have several issues. In terms of the Baxter trial finding at the early part of their trial that the prognostic factors were not distributed equally among the two groups. Number one is that when you do small trials, you have a greater chance of this happening. If you do a trial in the kinds of numbers that are going to be needed here, the probability that that will happen is very, very remote. Two, is if you do randomization correctly, you may need to do a stratified randomization to get certain key variables distributed. This all can be worked out. I think what happened was small trial, bad luck. What happens in these trials is if you have enough patients, those things work out as you increase the size of the study.

The other thing that happens with small trials is that you can sometimes in the same way you

had maldistribution of some of your prognostic factors, you can also see odd results where you start to see statistically significant differences between groups. But as your precision of your measurement of the outcomes increases as you increase your sample size, those differences in fact may go away or may in fact go the complete opposite way. there is a story that I learned when I was in England about the ISIS trials, which probably some of you are familiar with, which was some of the original thrombolytic trials. They talk about how early in that trial, the ISIS trial, that there in fact were statistically significant greater mortality in the thrombolytic group that obviously when they entered 10,000 patients all went away and was a mortality benefit for thrombolysis. So what happens with small trials is that you get results that can be wrong and can be misleading. The accuracy of your information becomes much more precise as the numbers increase. So the probability that if you do an adequately powered trial that this would happen is pretty small.

The second thing is that the trial of mortality -- I haven't done sample size calculations, but I guess if you are really dealing with a population that has a mortality of 40 percent, you could answer this question definitely probably with

1,000 or 2,000 patients. So the numbers are not -- I forget what that descriptive term is -- gargantuan or some other. I mean, it is an extremely expensive difficult trial to make happen, but it is in a sample size that is probably achievable.

I think some other outcomes or other common clinical outcomes you would want to study would be MIs. You would want to know what happens there. You would clearly want to know what happens with infection rates. There is obviously the immunosuppressive hypothesis related to allogeneic blood, and you would want to see how that compares with these new drugs. There are concerns about that.

So I think there are sort of standard clinical outcomes that few would argue are clinically important and that you would want to study as well. Thank you.

DR. ALVING: Dr. McKenzie, would you have any comments that you might like -- yes?

DR. MCKENZIE: Just to say that I think that some of the points that people in the audience might not realize is that in the management of trauma, the issues are time critical. The treatment and diagnosis occur simultaneously. We don't really know what the diagnosis is initially. And the opportunities for monitoring these patients are very

limited. So that this means it is very difficult to know exactly what the site and extent of the patient's injuries are. So as a result, heterogeneous populations are going to occur.

This also means that very simple measures are the only things that we can look at in the very early phase, and some of the things that have been suggested -- clearly, I think mortality is a primary outcome measure. We all know that. But if we choose the right secondary outcome measures, then we can also predict those patients that are going to die. So some of the things that the panel has already said, I would agree with. The use of lactate, the use of base deficit and the combination of the two as John Seigel suggested in a regression equation that actually predicts oxygen debt. Some recent data from Dr. Wyall looks at the use of sublingual catenography. Values of sublingual PCO_2 in excess of 70 are predicted to have a very high mortality. So that we can look at some of these surrogate markers and say if they are predicting a bad outcome, if we do something may change the oxygen therapeutics, maybe we can improve the outcome of these particular patients.

So, yes, I think there are simple things that need to happen in that first phase. Because it

is very difficult to gather any data when we don't know what the patient's problem is. So I would be interested in hearing more about this and also I am also interested to know about how people on the panel think we should deal with the situation where we use these oxygen therapeutic agents and where we know that, for example, thrombocytopenia is a known complication of the management of trauma.

Dilutional thrombocytopenia is obviously an effect of giving an acellular solution, such as all these products are. How do we deal with identifying that as a separate entity in the situation where we give these oxygen therapeutics to trauma patients. How do we identify if thrombocytopenia is the cause of the disease state or is it the cause of the product we are giving him.

DR. ALVING: Okay. I would like to ask Dr. Yarovostal to call Donna. This is just one brief announcement here. Thank you very much, Dr. McKenzie, we will keep that in mind. Let's move on to under B. Let's skip down to -- are any changes in the morbidity scores, such as the APACHE scores, are these changes an appropriate measure of morbidity outcomes? And maybe we could ask one of the panelists to just briefly explain the APACHE score and then give an opinion about the use of this in

trauma trials.

DR. HOLCROFT: I guess I can start, if you like. There are APACHE scores and APACHE scores. And to make a long story short, I don't think anybody puts any credits in the APACHE II, at least not for trauma patients. Now the APACHE III is a different story. The APACHE III has been validated with a large number of trauma patients in two independent trials, and it correlates well with mortality. It is expensive, however, because it is a proprietary instrument and you need computer power and you have to collect an enormous amount of data on the patients in order to accurately calculate it.

DR. ALVING: And can you say the type of data you have to collect? What are you looking for in an APACHE score?

DR. HOLCROFT: Well, the systems vary in expense from $20,000.00 to $40,000.00 I am told. The ones we use, they have been kind enough to give them to us, so I don't know the exact number. But it involves measuring just about everything you can think of for patients in an ICU. Now this would only apply to patients who are ill enough to end up in an ICU. So it goes all the way from electrolytes to Glasgow coma scale score to PAO_2 and FIO_2 indices and so on. So you have to enter an enormous amount of

data. Then you choose the worst value obtained during the observation period and from that you then calculate the probability of survival.

I can go on and on on this. Maybe I will just make one other point. At least in the trauma patients, the great -- well, not the great majority, but about 50 percent of the predictive value of the APACHE III score comes from measuring the worst Glasgow coma scale score recorded in the previous 24 hours. Or saying it another way, you can just take the Glasgow coma scale score and you've got 50 percent of the APACHE III in terms of its predictive value. And, in fact, you can even go further. You don't even need the whole Glasgow coma scale score, which is hard to calculate anyway in critically injured patients. All you really need is the motor score. So you can just get the motor score. You can just go in and ask the patient and see if they can wiggle their toe, and by that you have a lot of information about the prediction of survival. So that is both the strength and the weakness of it. On the one hand, it is actually fairly simple minded, which is good, in so far as you can learn a lot just by seeing how the patient is doing neurologically at 24 hours. But the weakness is that there are a whole lot of other variables that are not known in terms of

predicting.

DR. ALVING: Okay. I think one of the questions I would have is -- and we are going to get into this -- where are we going to give this blood substitute. We would really like to give it in the field, right? I mean potentially in the field, and then potentially if that is not possible, in the ER. Now can you make fairly accurate judgments in the field at that time? Is there a way to stratify patients?

DR. COHN: Just to make one comment in regards to Dr. Carson's comment. If we were to have a 40 percent reduction go to 35 percent with a 90 percent power, we would need 2008 people per arm -- per arm.

DR. ALVING: Okay.

DR. HOLCROFT: I'll respond specifically to your question. If you look at the Glasgow coma scale score again -- once again -- it predicts who is going to live and who is going to die, along with the systolic blood pressure. That is in the field. So if you have those two pieces of information, which will be available in most settings, you will have a pretty good idea.

DR. ALVING: Okay.

DR. RABINOVICI: I think that the

question that you raised here is a very controversial one. It is a subject of a lot of discussion right now in the trauma literature whether you want to really resuscitate patients prior to control of bleeding. There is an evolving concept that is advocated by Ken Mattox primarily and he published in the New England Journal of Medicine a couple of years ago a prospective study in which he has shown that pre-hospital resuscitation was not beneficial. This is also based on a variety of experimental data that show that when patients bleed -- or when you increase their pressure, they bleed more. So you exacerbate the blood loss and you exacerbate the shock stage and you exacerbate early mortality. Therefore, the question is really do you want to resuscitate patients prior to control of bleeding. And obviously the use of red cell substitutes falls within this question. The concept of what is called the hypotensive resuscitation or dry resuscitation -- dry resuscitation means don't give anything before you clamp the hilum of the spleen, for example, versus the hypotensive resuscitation, in which your endpoint is to resuscitate the patient let's say to a systolic of 80, but you don't want to push him any further knowing that that may be detrimental to the patient. So I can't tell you what is right and what is wrong.

I can tell you that the current ATLS recommendations are still to give fluids to patients prior to their arriving to the hospital. I would appreciate the comments of Steve Cohn or Jim Holcroft on that as well.

DR. ALVING: Dr. Cohn?

DR. COHN: I'll let Jim go first.

DR. HOLCROFT: Because I am known to have strong opinions on the subject? I don't know. I don't know. Although I think there are enough laws in the study that came from Ken Mattox's group that I don't let it influence the way I treat patients. On the other hand, I have to admire him and his group for conducting a trial that must have been extremely difficult to carry out.

DR. ALVING: Dr. Cohn?

DR. COHN: I certainly don't know the answer. I do know that animal work is seemingly pointing towards mean pressures that are lower than what we routinely resuscitate patients to in an effort to minimize blood loss in the setting of uncontrolled hemorrhage and probably with equivalent or better outcomes. So I don't think that Dr. Mattox's study has been validated, which would probably be required for us to make our trauma trial have, let's say, an alternative way of managing these

patients in the prehospital setting or in the hospital setting. We probably would have to go with the current national standard, which I guess you would say is to resuscitate people to some normal endpoint rather than let them be hypotensive with a mean of 40 or 50. So that is the way I would think about it.

DR. ALVING: Dr. Ness?

DR. NESS: It seems that you have shifted to this trauma C question, which is what to do when blood is not available. And it seems to me that even though eventually if one of these products is approvable, you could see that it would have great utility perhaps in the field. That to try to study it at this point would be very, very complicated and difficult, and that the less variables that you would introduce, which would be probably having patients appear at a trauma center where they can be fully evaluated and treated would be sufficient for the purpose of figuring out whether this material does carry oxygen as effectively or even better than blood, which is I think what we really want to know.

DR. ALVING: So you are for doing this trial in the controlled environment -- starting in the controlled environment of a hospital setting?

DR. NESS: The real issue is does this

material carry oxygen effectively, equivalently to or better than blood. And I think that the cleanest setting you can look at that would be the best.

DR. ALVING: Other comments? Dr. Joyner?

DR. JOYNER: Two things. One thing we know for sure is the faster people get to definitive care, the better they do. So I would hate to have anything happen in the field until you really had the kind of data Dr. Ness is talking about. I would hate to have anybody distracted out in the field from being put in the ambulance and taken for definitive care.

In Rochester, Minnesota, we actually do a lot of rural trauma care. We have a helicopter that goes a 150-mile radius. Even there, the amount of people who die from frank exsanguination seems to be pretty low. The main problems there are death from head injuries and motor vehicle accidents. A lot of the trauma is the people getting their arms and legs tangled up in farm equipment. It is not typically associated with exsanguination. And I think in general our patients would be better off there getting the helicopter to them faster.

DR. ALVING: Dr. Cohn?

DR. COHN: One brief comment. One of the things that doing a prehospital study would

absolutely mandate would be waiver of consent. And while I know that was done with the Baxter trial, I think that considering the results of that trial showed an increase in mortality, for us to advocate waiving patient consent would be an uncomfortable position to be in. I would rather see these patients or their surrogates or whatever give consent, recognizing that that already changes the population in many ways. Dr. Gould's group should be commended for the fact that they were able to get a group of patients with an average of 14 units of blood but get some form of consent prior to the patient going to the operating room. I think that is remarkable. But I think that if we were to advocate this in the prehospital setting, that you are mandating waived consent, which would make me very uncomfortable, at least in our institution.

DR. KRUSKALL: I wanted actually to ask the panel to critique the Baxter study. Because as I sit and look at it, aside from the fact that the endpoint was disconcerting, from what we have heard about it today and I have heard previously, it sounds like the type of trial that was extremely valuable in answering the question that we wanted to hear, even though the answer was disconcerting. So I wonder whether we should look at this as a model or at least

a good template for what we design, or are we trying to do something entirely different?

DR. ALVING: Would anyone on the panel like to answer that?

DR. JOYNER: How many sites were in the Baxter study?

UNIDENTIFIED PARTICIPANT: There were 18 with 17 enrolled patients.

DR. JOYNER: I am all for multi-center trials and I support the consensus with limited exceptions here about needing to go to mortality as an endpoint. But I think that the study design appears to have been fairly sound. But the more sites you have -- it is such a complex thing where everybody's trauma center is a little bit different -- is going to make -- controlling the uncontrollable is even going to be more difficult when there are 18 sites. So I guess if it were possible to try to focus on four or five really high volume sites and do that same type of study, I think that is one potential solution. Because with 18 sites, that is like herding cats. I mean, how are you ever going to get -- even if you get people to agree in theory to do all sorts of things, it is going to be very, very difficult to control that. Based on the talk that I heard, just keeping your eye on 18 balls is awful

difficult. I do a lot of studies in 10 humans and that is hard enough. To try and go and collect this data at all sorts of places where the traditions and the way they do things are different. So I think if you focus on -- the study design may have been fine, but I think you probably had too many sites among other things.

DR. WEISKOPF: I am not sure we -- given the time constraints of this meeting, I am not sure we heard enough about the study design to be able to make that judgment. We don't -- I didn't hear what the inclusion/exclusion criteria were. I mean, somebody who has a .22 in their brain stem is going to wind up dead, not necessarily from massive blood loss. There are many considerations that might go into a study design. What seems to be at the beginning or the front end a simple, straightforward study is actually in fact a very complex, difficult study design.

DR. ALVING: Okay. We've been going at this for some time now. We are scheduled for a 3:30 break. We could break. I think we should do that for the sake of the hemostatic system. We will now come back then at 4:00, at which time we will design the definitive clinical trials and we will then convene. So we will see you back at 4:00 and we will continue.

(Whereupon, at 3:30 p.m. off the record until 4:02 p.m.)

DR. ALVING: In order to help us discuss more about clinical trials and appropriate clinical trials in trauma, representatives from Baxter have volunteered to tell us more in-depth information about their trials. So we have Ed Sloan, who will discuss the U.S. trials, and Mike Saunders will give some more information about the trials in Europe. We very, very much appreciate your input.

DR. SLOAN: I'd like to just briefly review the inclusion and exclusion criteria for the U.S. trauma trial just so that people understand how that study was designed. We worked over two and a half years in developing with the input from many practitioners. We intended to include 850 patients who either had presumed or presumptively had hemorrhage and were hypoperfusing despite prehospital care. So the study was based in the hospital. Our means of assessing that the patient was inadequately being perfused were three-fold. The patient either would have a systolic blood pressure of less than or equal to 90 and a pulse of at least 120, both of those, or they would be hypotensive with a systolic blood pressure less than or equal to 90 with a preterminal rhythm, that is a pulse less than 60, or

third, a base deficit of greater or worse than 15 meq per liter. As it turned out in the study, probably 85 to 90 percent of the patients actually were enrolled because of the first criteria, hypotension and tachycardia. The patients were expected to have a 40 percent mortality overall in aggregate.

The exclusion criteria that are important and relevant to this discussion are the following. Patients who had significant traumatic brain injury were to be excluded. We said that if you believe there is a space occupying lesion that would significantly impact the patient's outcome, try to exclude them. We believe that in the study up to 15 percent of the patients would be believed to not have a lesion and indeed would have a lesion. In fact, in the study about 15 percent of the patients did have significant traumatic brain injury with an AIS score of 4 or 5. Also, those patients for whom death was felt to be inevitable were to be excluded. That is, if the practitioner looked at the patient and believed that no matter what they were going to do, the patient would expire, then they were asked not to enroll those patients. Also excluded were patients who had had an injury up to 4 hours before the time they were to be infused. That is, if they had survived long enough to make it four hours, it is not

likely that their mortality risk would be so high that it would be appropriate to include them in the study. We made no limitations or we did not stipulate how much prehospital therapy the patients could receive. We did not exclude patients who perhaps may have come in by helicopter transport, although that represented a very small number in the study. We did not preclude the use of blood. We did not mandate how the patient was to be treated and we did not mandate what endpoints to which the patient was to be treated with standard therapy. We did, however, modify the way in which the patients were treated based on whether or not they continued to meet criteria. All patients received 500 cc of DCLHb. If they continued to meet the entry criteria, they could receive up to another 500 cc. However, if they compensated and no longer met entry criteria, we asked the investigators to discontinue the use of DCLHb. And in fact, probably two-thirds of the cases of patients only received 500 cc of DCLHb because after this initial infusion, they no longer met entry criteria and they were felt to have compensated clinically. This information actually hopefully will be published this year. So you will be able to get more information through the article.

DR. WEISKOPF: A quick question. Since

your entry criteria were based in large -- one of the major entry criteria was systolic blood pressure. And since the product itself increases blood pressure independent of -- in addition to its volume effect, it increases blood pressure -- do you think that this negatively affected the study because patients might have been inadequately resuscitated in terms of the total amount of intervascular volume?

DR. SLOAN: It turns out that the blood pressure change that was observed in the control group didn't differ significantly from the treatment group. Is it possible that patients could have been under-resuscitated because of the pressor effect of the hemoglobin solution? Yes, that is possible.

DR. HOLCROFT: One other question if I may. You defined serious head injury as those patients who in retrospect had abbreviated injury severity scores for the head of 4 or 5. And then in addition, most of the patients were hypotensive when they were entered in. How many patients had the severe head injuries in the treatment group and how many in the control group? What were the numbers?

DR. SLOAN: One moment, please. Using Glasgow coma scale score, a GCS of 3, the most severe category, was seen in 38 percent of the hemoglobin patients and 26 percent of the normal saline

patients. Given the small sample size, that was not statistically significantly different.

DR. HOLCROFT: And the patients who in retrospect had severe head injuries? Do you know those percentages between the two groups?

DR. SLOAN: With regard to AIS scores?

DR. HOLCROFT: Right.

DR. SLOAN: One moment. I don't have that specific data here.

DR. HOLCROFT: Okay.

DR. SAUNDERS: Just to add a number to what Dr. Sloan had just presented. With the systolic blood pressure, I believe it was actually a 2 mm mercury mean increase compared between DCLHb and the control group in the first four hours after admission. So, again, I agree with that, a very small amount.

What I wanted to do is just very briefly present some of the features of the HOST trial again, the European trauma trial, and particularly to point out some of the distinct differences. The principle one is that this amounted to an administration of the product more immediately. It was given on scene. In Europe, physicians travel in the ambulances. And because of this factor, we were able to enroll patients on site and began resuscitation immediately

with the hemoglobin solution. So there is a big difference there.

The other big difference was that we were looking at morbidity endpoints rather than mortality. SOFA scale scores were used as a measure of benefit for the product. As far as the inclusion/exclusion criteria, I have limited information here primarily because at an on-scene evaluation, you have limited access to other diagnostics and you have to make it largely on clinical judgment. Males and females 18 years of age or older with probable hypobulemic hemorrhagic shock class III to IV resulting from evident or presumed severe hemorrhage, a systolic blood pressure of less than 90 mm of mercury and obvious severe trauma, and that they were being transferred to a hospital that participated in the trial. Those were the basic inclusion criteria for the patients. Any other questions? Yes.

DR. KRUSKALL: I am confused as to why you say you are not looking at mortality. I know morbidity was the primary endpoint, but you tabulated and reported mortality in the European study.

DR. SAUNDERS: Yes, we did. And that -- five day mortality was part of the multi-organ failure score, the SOFA score. In addition, we had secondary endpoints where we were looking at

mortality after 28 days and there were some morbidity measures as well. The primary reason that I highlighted the mortality for the HOST trial was because that was the major concern that was expressed by not only the FDA reviewers but also the European medical reviewers for the regulatory agencies. So that was a significant concern that they expressed.

DR. KRUSKALL: And so if I contrast the differences, the European trial must have included more patients because you were less likely to have said that death was inevitable on the scene I suspect. And also there wouldn't have been that four-hour period for an injury to be older than that time interval. And perhaps you included more traumatic brain injuries as well?

DR. SAUNDERS: I can't recall as far as the traumatic brain injuries were concerned. There were 121 patients who were admitted to the HOST trial as opposed to the 98 that were admitted to the U.S. trauma trial.

DR. WEISKOPF: For the U.S. study, can you please describe the randomization process and in fact in practice how it worked out at the institutions?

DR. SLOAN: The randomization was in blocks of six. It was blinded. When a patient met

entry criteria -- and that had to be within 30 minutes of meeting the vital sign criteria in the hospital -- the research team would go to an envelope. They would initial it signifying that they were about to open it. At that point, once the envelope was opened, the patient was randomized to whatever treatment was in the envelope. And in the intent to treat analysis, anyone for whom the envelope was opened, even if they didn't receive therapy, they were analyzed in the summary results.

DR. WEISKOPF: So each institution was randomized separately, is that what you are saying?

DR. SLOAN: Yes. And it was in blocks of six so that it would evenly distribute through blocks of six.

DR. CARSON: Were there any mistakes made with randomization? You know, were things always in order? Did you notice any problems with that?

DR. SLOAN: I believe there was one case when a patient assigned to receive hemoglobin received saline and there was one case in which the patient was assigned to receive saline and they received hemoglobin or vice versa. There was one case of inadvertent wrong administration -- one in each direction.

DR. KRUSKALL: Was there any opportunity

for the caregivers or for relatives to remove the patient from participation after assignment to an arm, and how often did that occur? For example, was there a systematic bias that would have excluded patients from one arm or the other based on that type of refusal?

DR. SLOAN: It did occur in 14 cases that patients were randomized but were not infused. The investigators were instructed that in-between the time in which they were randomized and the time they could be infused, knowing it might be 10 to 15 minutes, if they met an exclusion criteria, they were not to be infused.

DR. JOYNER: When you look at your sites -- you had 18 sites. What were -- did all sites enroll at least one patient or did you have a couple that really stood out and enrolled a ton?

DR. SLOAN: One site enrolled no patients because they had just finished the informed consent process. But all the other 17 sites enrolled patients. The majority probably were in six sites.

DR. JOYNER: Were the outcomes any different in the six sites that enrolled the most?

DR. SLOAN: Study site appeared not to have an effect on outcome. We looked at that specifically in the a priori designed analysis.

DR. NESS: A question about the study. I was on the blood products advisory committee when some of the issues were discussed. And it seemed to me at that time that even though this is a trial of an oxygen carrier in a trauma setting, which is obviously relevant to what we have been talking about, the doses that you were planning to administer would not be enough so that you could have made a comparison as to the efficacy of the blood substitute compared to a red cell resuscitation. Is that fair or is that true?

DR. SAUNDERS: Yes, that is fair. And the presumption was that this product -- this goes back to one of the original theories with DCLHb that the vaso activity was actually a product or a facet of the product that added to its efficacy.

DR. NESS: I just wanted to bring that up because I think we may be making more of this is an example of the kind of trial we want to have it be than it really was.

DR. ALVING: Well, thank you very much for providing that extra information. We may have to call on you again. Why don't we go to C. And, yes, I did skip one question in B, but it was too complicated. I wasn't even sure what we were to discuss. Let's say it is a highly refined question

or highly distilled. It is one that we can get to after we have designed our put forth ideas for clinical trials. But let's ask now, in situations where blood is not available, should the product be tested in actual acute blood loss situations to demonstrate impact on survival? And specifically, to what -- I think the panel feels very strongly that certainly we are not ready for a field trial at this time. And as we heard with the Baxter presentation, there were certainly different circumstances in Europe. They have a different system that made it more feasible there. But to what extent can data generated in an ER or OR setting be extrapolated to a rural setting where there could be a substantial delay to definitive care? Let's say that a very fine trial is done in the U.S. and at least equivalency is shown, can this then be extrapolated beyond that? What is the opinion of the panel here?

DR. HOLCROFT: I guess I am willing to start. If it is equivalent -- if it can be shown to be equivalent or safe, if you will, in the emergency department or in the operating room, then I think it would be -- I think it would be desirable and necessary to study it in a situation in which it really has a chance of helping somebody. And I would make one observation. We have said that in Europe

because -- at least in Germany, where they have sophisticated physicians riding the ambulance rigs and going out in the helicopters that they can conduct studies that we would have more difficulty doing here. But I would point out that the nurses who ride on some of these helicopters and the paramedics who work in some of these ambulance rigs are very sophisticated observers. They are as good as a surgical resident in terms of resuscitating patients. I mean, those are the facts. In selected centers, you can depend on those nurses to do the right thing. Which also means that you can depend on them to collect data for you. So I think it can -- I think you can do field trials once you have a product that you feel fairly comfortable that it is safe, so that you can enter patients in the trials without informed consent.

I would make one last comment. The business about informed consent is a tough one. Now clearly if you are going to do a field trial, you are not going to have informed consent. But I daresay if you are going to do a trial in the emergency department, for practical purposes you are not going to have informed consent either. I mean, those are the facts. And for those of you who haven't taken care of a trauma patient in the emergency department,

the patient is brought in and they are in shock and they are afraid, they are cold, and some of them can't respond. They are entirely at the power of the physicians taking care of them. So if a physician says to an individual like that, a patient who is afraid that he or she is going to die, I'd like to enter you into this trial, I can guarantee that the patient is going to say yes, and that is not informed consent. So you might as well just face up to it. If you do trials under these circumstances, you are going to be doing them without informed consent. And you can do it in the field or you can do it in the emergency department. It amounts to the same thing.

DR. RABINOVICI: I have a problem extrapolating from the ER/OR setting to a rural area, because I think that the management is different. Patients who are in severe shock and there will be always initial resuscitation and evaluation and then followed up by definitive control of bleeding, and I think this is not the setting in a rural area. In a rural area, we will resuscitate them, and there will be some kind, if you will, of natural selection of patients. Because you don't provide the definitive control of bleeding. So I don't think you can really extrapolate from these two scenarios.

DR. VLAHAKES: There is also an issue of

adding an important confounding and difficult to quantitate variable, namely adding in that time interval. In the sort of discussions that took place outside, we were going over some of the considerations with respect to powering the study and numbers of patients. And already this may be a challenge in terms of the number of individuals. So if you add a complex variable that may vary over a broad interval and impact significantly on outcome not necessarily related to the test article, it may really make the study pretty messy in terms of analysis.

DR. WEISKOPF: Jim, with respect to informed consent, I agree with you with one exception. And that is many institutions for patients to be treated in the emergency room who can neither appropriately respond or as you say are so subjectively influenced that their consent is truly not informed will appoint a patient advocate who you call and explain and they will make an instant response for the patient. I am not sure how many institutions have that, but I know we have done that sort of thing in the past.

DR. JOYNER: About the rural setting. I agree with Dr. Vlahakes. I don't think you would want to include that in any kind of initial study,

because that would just make a difficult study even more difficult to do. But there are a couple of places in rural areas where this stuff could be quite useful while you are waiting for definitive transport. But again, I think the thing you want to always do is do nothing that would inhibit transport. I am thinking about unexpected obstetrical bleeding where some family practitioner is delivering babies out in Byron, Minnesota or someplace like that. Once in a while, they are going to have problems. And we have seen people in the ER with very low hemoglobins and fortunately they have been young, healthy women. I can't remember anybody who has died, but it is certainly possible. But that would be the most routine type of situation. You don't know about traffic accidents. Because typically when the traffic accidents occur or the farm accidents, they just call us directly and we dispatch the helicopter immediately. People are not transported from local hospitals to St. Mary's Hospital in Rochester. They are transported from where they are via our helicopter. And occasionally there is a local ambulance with some EMTs nearby.

DR. CARSON: How common a problem is this where -- you know, this concept of rural? Is this really an issue that is going to come up with any

regularity? I mean, relevant to that, of course, is the importance of the question and second is the feasibility of doing any kind of studies. If it is not common enough, then you are not going to have enough sample to study. I don't have any sense for this. Can the surgeons tell me about that?

DR. JOYNER: I don't think you can study it. But I think it could potentially be beneficial for people in those situations.

DR. HOLCROFT: We looked at the data for the State of California because at one time we put together a proposal for the NIH in which we enlisted the California Highway Patrol, which enjoys a very good public image in this state, and they were willing to use their helicopter system to enter all the patients in the state in rural areas whom they transported. And it turns out by a power analysis, we could have entered it, but it would have required a statewide effort with the cooperation of a state agency to achieve it.

DR. CARSON: Can I raise another population. I don't do this clinically, so I need those who do to comment. But it strikes me that even in major cities where the gun and knife club are at work on Saturday nights, that if the emergency personnel get to a scene of that sort and stuck a

line in and then infused one of these drugs as that patient is being transported to the emergency room that that might benefit them. I have heard comments to say that if that takes any significant time, then that is probably not good. But would there be situations where that potentially could be lifesaving by infusing oxygen-carrying fluid to maintain them until they get to the emergency room?

DR. HOLCROFT: These guys are amazing what they can do in helicopters and what they can do on ambulances. I am referring to the paramedics and the nurses. They get IVs started without delay in transport in many cases.

DR. CARSON: So then that would suggest that maybe you could -- instead of hanging saline, you could hang one of these fluids and that conceivably could make the difference. I mean, instead of -- it means abandoning the rural model but going to the major cities, which of course has the obvious advantages. So if these patients were brought to Hopkins, which probably is a community that might have lots of these kinds of patients, or the University of Maryland where there are big trauma centers -- or Miami seems like a natural place, at least it has the reputation. Would this be a model that would emulate the rural question and one which

would be much more applicable to a much larger number of people in our community?

DR. KRUSKALL: I worry that we won't be able to construct an adequate trial. If it takes the State of California, the entire state, to even begin to plan something like this -- what I am concerned about is that this could be an easy back door entrance for acceptance of one of these components before in fact we have done the proper clinical trial within the ER/OR setting. So I am a little worried to think about it here before we really understand a trial that allows us to see efficacy and safety in a more formal study system.

DR. NESS: I have two comments. First of all, it is not only a Saturday night problem. It is all week. But the second comment is I think we are mixing what would be useful for an approved product versus what we ought to do in initial studies to see if this is a physiologically effective therapy.

DR. RABINOVICI: I think we have touched upon that earlier, and I really can't tell you if giving some fluids prior to control of bleeding is a good thing to do. I think the data is not there. I think that most of us just follow the training we got in our practice for years and there is no adequate evidence in the literature to suggest that we reverse

course here. On the other hand, I am sure that many of us cared for patients who became hypotensive and didn't bleed much and allowed you to control bleeding in an easier fashion as compared with when you massively resuscitate a patient, you bring the pressure up and suddenly they start bleeding and your repair becomes more difficult and then the time from injury to control of bleeding, which I believe may be the most crucial endpoint, is compromised.

DR. ALVING: So I think maybe to summarize in Section C, what the panel seems to be saying is that a first trial in trauma really needs to be done in a controlled setting -- OR or ER -- and assuming this would be an equivalency trial with endpoints of mortality and possible secondary surrogate endpoints that have been mentioned such as lactate measurements, base deficit measurements. But also I think neurologic outcome could be one of those other measurements. But that the data obtained here could not really be extrapolated to the rural setting or the ambulance setting, and that again might take another trial to really test out effectiveness in the field setting where you do have questions about resuscitative fluids. Is that pretty much the consensus? Does anybody want to add anything to this before we move on to D? We are moving on -- pardon?

Well, in the military.

DR. HOLCROFT: I'd make one comment. On the one hand I can understand why using these solutions in the field is hazardous or in combat casualty situation. But on the other hand, this is precisely the situation in which these solutions might do the most good.

DR. JOYNER: I think if you look at the data from the military, if they had a product like this, it becomes very complex calculation, as I am sure Colonel Hess would tell you about. How resources are allocated -- it becomes very calculated in about who you think you can help and who can be transported and get the definitive care. There is a limited number of people who just aren't -- there is a lot of people who can survive and you have a few minutes with or some time with who you think can get to someplace where they can get some treatment. Then there are a reasonable fraction of people, as Dr. Silverman pointed out, who are blown up or have unsustainable injuries. So then it would be up to them to calculate what that small group in the middle is, what the resources they want to devote to that are, and whether they have a product that would actually potentially help those people or would they be better off devoting those resources to better ways

to transport those individuals.

DR. WEISKOPF: I don't believe the question is a particularly useful or important one because in fact you cannot study -- if any of these compounds are approved or even in trial, you couldn't study them in a military manner. And so if one of these compounds does get approved and shown to be efficacious and safe, the military is going to use it. And if it is not shown to be efficacious or safe, they won't use it.

DR. ALVING: Well, I think that this is certainly a very complicated issue and certainly Colonel Hess knows this very well as do others who have been in the military for a long period of time. Certainly I think military challenges are constantly changing depending on the terrain, the reason for the military to be where they are in the first place. So I think we could leave that -- actually leave it to the expertise of the military, many of whom are here today and actively listening. And I think maybe some of the first challenges would be to show safety efficacy or at least equivalency to red cell transfusions in a controlled setting where measurements can be made. But I must say, many of the challenges faced in the military are not that different from the challenges faced by physicians who

practice in Baltimore, Miami or any of the larger cities. So I really see that our battlefields are really civilian battlefields, and I think if we can do good trials in that arena that this can help the military to some extent. It is going to be a matter of time you get to definitive care and other such issues that really blend civilian issues with military issues, although the types of trauma may be different in many situations. Colonel Hess, do you want to add anything to that or make any comments?

COLONEL HESS: Just that I believe that the Army wants these products tested in a reasonable developmental way. We would like the demonstration of efficacy, effectiveness, availability and efficiency in the very standard way you do that. Efficacy, can it work? Effectiveness, does it work? Availability, can we make it available to the people who might actually use it and benefit by it in some cost effective way? And finally, is it worth doing? You know, the real benefit analysis.

DR. ALVING: Thank you. Let's move on. Dr. Silverman, after you've made your comment.

DR. SILVERMAN: Thank you. I just wanted to say that the questions here were tiered to start with the most closely monitored setting and moving progressively further away, with the ultimate

question being the last one, efficacy in the military. That accounts for our questions about a rural setting, where there is a delay to definitive care. We also asked a question about using an oxygen therapeutic in an ambulance setting, by which we meant an urban ambulance setting, and we viewed that as having somewhat different issues from delay to definitive care. Although someone pointed out to me just now that in New York City, that might have the same delay to definitive care as you have in the rural setting. In any event, these were tiered questions, backing away from controlled settings out to the least controlled setting.

DR. ALVING: Thank you.

DR. CARSON: Can I make a comment?

DR. ALVING: Yes.

DR. CARSON: I have been advocating for mortality trials that are large. But I also want to advocate for trials that are simple. And this is very contrary to the approach that most of the FDA-oriented pivotal trials are designed. They are designed to collect enormous amounts of information on every single patient, and that makes -- and what the companies are responding to is the expense of doing that, of course, and the logistics of doing that. but I would argue that the FDA can make that

easier for them by making data collection much more simple and making the amount of information that you can gather on each patient only the essentials and that you not try to collect this enormously detailed information on every single case, but rather go for clinically important outcomes that we all understand and accept that you are not going to collect every little piece of information, but by doing it this way, you are going to get the precise answers to your major questions and give up maybe some of the smaller issues that maybe you get in post-marketing surveillance. But that is a different philosophy than the FDA has normally taken, at least that is my understanding. And that might make it more achievable to randomize a lot of patients but keep data collection much, much simpler.

DR. ALVING: Thank you. Let's go to D now. In situations where blood is available, can clinical equivalence in mortality between an oxygen therapeutic and blood be a basis for licensure? Any comments by the panel? And then we will get to the next question after that and that will be it for the day. Do you believe in the equivalency issue? Dr. Vlahakes?

DR. VLAHAKES: I'll give the short answer, yes. And this has to do with simplifying the

study design, and I agree with the comments about making this kind of study as easy to do as possible. That early resuscitation time upon arrival to the facility is very dynamic. It is also a time when the relationship between the number of events and documentation is a lot higher than it would be for other kinds of clinical endeavors. So I think if you wanted a very straightforward design that was very doable and what I call an integrated outcome parameter, death, which also includes -- there is an element of safety consideration in there, and showing that equivalence could certainly be a basis for licensure.

DR. WEISKOPF: I would say it depends. It depends greatly on study design. For example, let's take the Baxter study that we have been talking about. In that study, my understanding is that they gave 500 ml of the product. Now suppose -- let's say that study went on to completion and there was, in fact, no difference in mortality between the treated group and the control group. Having given 500 ml of the product let's say in patients who went on to have an average of 6 of 8 or even 10 units of blood, would people here say that that is satisfactory for determining equivalence? I wouldn't. I would not be happy with that. Because that means that the treated

group would have then had say 9 units of blood and 1 unit of the product, and the control group would have had 10 units of blood.

DR. JOYNER: So Dr. Weiskopf, are you saying that if we are going to do this -- if you are going to get on the horse, you've got to ride it until it is over? And you have an arm where all they get until they have surgical control of the bleeding -- one arm gets blood and one arm gets blood substitute?

DR. WEISKOPF: Well, that would be another extreme. There might be some middle course. But I am saying that I think the study -- I think we can obviously now talk freely about it because the study is over and Baxter is pursuing other interests in this area and not that particular molecule. That study was not designed to show efficacy.

DR. AEBERSOLD: The Baxter comparison was saline. So it was blood versus saline. Both arms got red blood cells as the investigators deemed necessary. And this question is designed about a trial that would compare resuscitation with blood substitute versus red blood cells up to control presumably of the bleeding. These things are -- all patients are going to need red blood cells eventually. So the Baxter trial is not the trial

design we were talking about in this question.

DR. JOYNER: Can I ask -- Dr. Gould, how do you guys do it? You kept going and going and then eventually when you get to 20 units, you quit and then they get the red blood cells or do they get them concurrently? What is your strategy in your transfusions?

DR. GOULD: Once we start, we keep going until they achieve that dose. The only reason we don't -- the infusion stops when we reach the maximum dose -- remember, that has worked its way up -- or the bleeding stops. If we are -- at the point we are now, a patient can get 20 units. But if the operation is over and they only got 6 or 2 or 8 or whatever, that is it. We are not really continuous.

DR. JOYNER: So now you have -- in the current way you are doing it, you have a collection of people who get 20 and continue to get transfused after 20 because they continue to bleed?

DR. GOULD: Well, as Dr. Aebersold -- anybody who gets 20 is going to need red cells.

DR. JOYNER: Right.

DR. GOULD: If they are still bleeding, they get it in the OR. If they are in the recovery room and have 20, sometime over the next two or three days, they will get red cells.

DR. JOYNER: But then there are some people that you get lucky with and you give them 2 or 3 units and you get the bleeding stopped and that is it?

DR. GOULD: Correct. And many of them don't get anything.

DR. JOYNER: So would an arm be some strategy like that, have some maximum upper limit dose of however many units it would be compared to blood only?

DR. GOULD: Dr. Cohn says why have an upper limit.

DR. JOYNER: But to pursue a strategy, assuming it is safe and tolerated, you can just keep pouring this stuff in while it pours out?

DR. GOULD: Again, it depends on -- what question are you asking?

DR. JOYNER: We are trying to say what is the optimal simple study design?

DR. GOULD: To answer what -- I understand that question. But what is the question the study should answer?

DR. JOYNER: Are red cells and the product equivalent in the treatment of acute trauma?

DR. GOULD: Based on no difference in mortality?

DR. JOYNER: No difference in mortality. Using a simple criteria.

DR. GOULD: Well, the question is -- that is what Dr. Aebersold I think was saying. You have to get it all out on the table. What sort of patients do you want to accept? Those with a 10 percent, 15 percent or 20 percent mortality.

DR. JOYNER: Right.

DR. GOULD: And what delta do you want to assess? How much of an increase in mortality in the treatment group do you care about? Because that is what we are talking about with equivalency. How much higher than the control group can the treatment group be? You are not talking about lowering mortality. Is that half a percent? 1 percent? 2 percent?

DR. JOYNER: When is it not statistically different and when do you --

DR. GOULD: That depends on what delta you are willing to accept. The numbers are humongous.

DR. COHN: Well, we just looked at this. With a 95 percent power, if you are going to reduce 40 percent to 35 percent, which would be about a 10 percent reduction, you need 2,474 patients per arm. If you are willing to have a 25 percent reduction accepted at a 95 percent power, you are talking 40

percent to 30 percent, then you need 600 patients per arm.

DR. GOULD: But I don't think we are talking about 40 percent mortality. I think the more realistic way to get a study done -- just to get -- practically. I am not talking about whether that is a good idea. To be able to feasibly do the study based on our experience, I think you are talking about a mortality in the 15 percent range, where you can actually get patients. And now you want to see if you can detect whatever the panel agrees is an acceptable increase, and the numbers based on our projections go up 20,000, 40,000 or 60,000 patients per group.

DR. COHN: I completely agree. And I want to just comment that when the patients come in and they die on admission that that eliminates a large percentage of the people that die from hemorrhagic shock. And obviously the people that come in code and die right there are not people you are going to enter into any kind of a trial. So I think the mortality that we are talking about in the control arm is going to be considerably less than 40 percent.

DR. GOULD: I think it will be in the 15 percent range. Dr. Holcroft is agreeing to.

DR. HOLCROFT: Like 5 percent if they don't have head injuries. Those are our data.

DR. GOULD: Well, okay.

DR. HOLCROFT: So if you make it into the hospital and you are alive and you don't have a head injury, you have a 95 percent chance of surviving across the board.

DR. GOULD: The issue with that is that that likely shrinks even more the increase in mortality that you are willing to accept, which doesn't help your powering or your sample size. So it is a dilemma. It is -- I appreciate the efforts of the panel to say equivalent sounds fine, but we have lost a lot of sleep and a lot of hair, some of us, over trying to sort this out. Some of the guys on the panel too. You must be thinking about the same thing.

DR. CARSON: You've grown some extra too, though, Steve. Steve, before we let you off the hook since you brought this up -- if you were to work with the 15 percent -- I have never done sample size calculations, so I would have to do the numbers. So if you started with a 15 percent mortality -- he has got to turn on his computer.

DR. GOULD: I have a slide that I will put up that might be useful.

DR. CARSON: An equivalence trial is equivalent to a 95 percent power.

DR. GOULD: And I did it with the power of 80 percent. So it is going to be even greater. We have got one slide. 15 percent mortality with alpha of 5 percent and power of 80 percent, with an increase in the mortality of 0.5 percent.

DR. JOYNER: It is going to make things worse.

DR. GOULD: Well, the question for equivalence as we understand it is that the FDA nor any of us should care if it makes it better. We are asking the question only because we don't want to make it worse. It is going to be 64,000 and something per group. So that will take more than a week.

DR. JOYNER: We know what to do with the budget surplus now.

DR. AEBERSOLD: Steve, let me just put the question in numerical terms. If you have 15 percent mortality, as Dr. Gould is saying, in the control group, and you have another group that is getting a blood substitute as needed until bleeding is controlled, and the point estimates are the same -- I mean, 15 percent mortality -- the second part of the question gets down to the numbers. What would you

want to see as the -- what would you want the confidence intervals to rule out in the way of an increase in mortality. Would you feel comfortable if you could say, well, we had an identical point estimate but the data only speak to ruling out a 20 percent mortality and it could be as much as 5 percent worse. Would you be willing to use that product not knowing that the true mortality may not have gone up from 15 percent to 18 percent and actually in the long run people would be dying? Or would you want to say you want to rule out 15.5 percent? That is when you get to a number like 64,000 patients.

DR. GOULD: Correct.

DR. AEBERSOLD: What about 15 percent to -- do we have the slide yet? Then I can stop talking. 15 percent to 17 percent.

DR. RABINOVICI: Steve, I am not sure where did you get this 15 percent mortality? I mean, some of the patients that were enrolled I believe in your study and also in Baxter's study definitely had Class IV hemorrhagic shock, so the mortality of these patients is much higher than 10 or 15 percent. I think that you are talking in fact about two types of patients, and there is I think an evolving recognition in the trauma community that trauma

patients are divided into two classes. Those with uncompensated and those with compensated hemorrhagic shock. And those with uncompensated, these are the patients who will have severe hypotension, tachycardia and no urine output. And those patients who have compensated hemorrhagic shock will have most likely normal or near normal vital signs, but still the major problem will be the redistribution of oxygen delivery. And I think that those in severe hemorrhagic shock, it would be extremely tough on you to show any worsening or improved mortality. I think those patients with compensated hemorrhagic shock, these are the patients that you should be aiming for. And this would be my recommendation to this panel.

DR. GOULD: Here is the table. And as I said, it reflects a lot of thinking that has been done. So this is the sample size to detect a difference, which is what we are talking about. Well, you -- it may be -- okay, go ahead. If the mortality rate we put on the table -- we have done all the way up from 1 percent to 20 percent -- and down here is the increase in the treatment or experimental group that is allowable. So in some of our discussions we have said -- because our mortality is 15 percent. If we want to have no more than 15.5 in the treatment group, a one-sided test is

appropriate because we are not really caring about a reduction. The question is are you increasing mortality. And at the power of 80 percent, this is the sample size per group. If you accept a 1 percent mortality as the upper limit, if you want to be certain that it is no more than that, it is 16,000 and down to so and so. If you will accept a 5 percent increase -- up to a 5 percent increase, you can do it with 750 patients per group. So I think the 2,000 number for -- I can't remember what numbers you talked about before. When you had a 40 percent mortality. I don't remember what delta you are talking about -- 2 or 3 percent. It is in the single digit thousands per group. You know, we can all go to our statisticians -- and I am not a statistician -- and we may get different precise numbers. But I think -- because we looked at this a bunch of different ways. They are all in this ballpark. I mean, they are not realistic numbers. If you want to achieve that level of statistical certainty.

DR. KRUSKALL: You know, we may have to use common sense as well as statistics. If you go back to the Baxter trial, there was an increase in mortality, but there also was an increase in serious adverse events.

DR. GOULD: Yes.

DR. KRUSKALL: And it strikes me -- and I am hearing Dick whispering variations on the same thing -- that although it would be wonderful to put our bets entirely on mortality numbers, that although mortality is important for both efficacy and safety, I also would be interested in very strong secondary endpoints as to oxygen carrying ability and the absence of serious adverse events like organ damage. If you gave me mortality figures and you worked at a 2.5 or 5 percent difference, your power calculations and your study size were limited to that, but you also told me that there were no differences in serious adverse events between the two arms and that oxygen carrying, to the extent that one was able to measure that, was equivalent, I would have a lot more confidence and ability to swallow a mortality difference than I would be in the absence of those additional secondary endpoints.

DR. GOULD: Yes. You know, this is all fine in the abstract. The approach we have taken -- and I think when Mike reviewed the Baxter stuff this morning, one of the lessons that they learned was that the preclinical models should validate what you are going to do. I have no basis, based on our preclinical data, to anticipate a reduction in mortality if I compare the use of Polyheme to the use

of blood. I have no basis to think that. I am not sure, short of some data -- I don't want to distract this session right now -- that Steve Cohn and I discussed that was presented at a trauma meeting last week, I am not sure I can make a strong argument that we are going to see a reduction in SAEs. I would like to think I would, but I am not sure I am confident enough of that to go design the trial. Which leads me to again say why we took the approach we did, which is to address the situation of reduction in mortality when there is no alternative. And I heard all of the comments this morning about the need for concurrent controls, and I respectfully disagree. Dr. Carson, Dr. Holcroft, Dr. Cohn, Dr. Ness, and I expect you Margot would say that all the progress that has occurred in the last 10 or 15 years, when bleeding patients' hemoglobins get below 3, they still have a high likelihood -- and Dick Weiskopf too -- have a high likelihood of not dying. And I can't do that prospectively. I can't withhold red cells. So that is how we feel we have assessed the reduction in mortality. And at that point then assessing the safety becomes much easier, as Dr. Silverman has suggested.

DR. CARSON: When we talk about an equivalence trial, we are not talking about showing -

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DR. GOULD: That is not an equivalence trial.

DR. CARSON: No, I know. But see, we are not talking about trying to demonstrate a benefit.

DR. GOULD: I understand.

DR. CARSON: We are just trying to show --

DR. GOULD: The lack of a --

DR. CARSON: That these folks don't do worse.

DR. GOULD: It is the lack of a detriment. I understand that.

DR. CARSON: Right.

DR. GOULD: And I don't think that is an achievable study.

DR. CARSON: Well, these sample size -- and these sample size calculations are -- if you were to do an equivalence sample size calculation, it is 95 percent power, not 80 percent power.

DR. GOULD: So what does that do to the sample size? It is not going to make it smaller.

DR. CARSON: Oh, no. No, it makes it much bigger.

DR. GOULD: All right. So let's take Dr. Holcroft's 5 percent. At 5 percent, you want your

increase to be even smaller.

DR. CARSON: Right.

DR. GOULD: So -- all right. You've reduced us from 64,000 to 25,000 per group.

DR. HOLCROFT: I am trying to help. But the way I would look at it is specifically with question D, if equivalence could be shown, would that be a basis for licensure? And I would say, no, for me. But if you could do a reasonably sized trial that showed that there wasn't much increase in the detriment -- maybe 1 percent or something -- and I would try to choose a percentage that would give you a reasonable chance of demonstrating that, then I would feel comfortable at least randomizing patients into a trial without informed consent in a situation in which the product really couldn't be expected to save lives.

DR. GOULD: But, Jim, at a --

DR. HOLCROFT: Like a prehospital trial.

DR. GOULD: But at a mortality of 5 percent, how much of an increase would you be willing to accept.

DR. HOLCROFT: Well -- you see, I would enter patients with head injuries. Because there, you see, I think you can really help some patients. Now if you do that, then you can get your mortality

rate as high as you want. So it depends which patients you choose to enter into your trial. You can either choose a real high mortality group, which will be your patients with head injuries, or you can choose a patient with a low mortality group. Pay your money and take your choice. So you can select that percentage. But assuming once you've done that, then I would be -- if you've shown with a reasonable sized trial, a few hundred patients in either arm, that it was just maybe within 1 or 2 percent or something of the control group, then I would feel comfortable entering those patients into a randomized trial in the field where you can anticipate some real benefit from the solutions. So to answer your question, a couple of percent.

DR. GOULD: With a high mortality rate in the control group.

DR. HOLCROFT: Well, let's take the 15 percent mortality rate. That would be reasonable. So I would go down to maybe 2.5 percent -- there we go, 500 patients in a group. Something like that.

DR. GOULD: 5,000 patients.

DR. HOLCROFT: No. For the equivalency trial, I would design it -- I would just try to be practical. I would say what is practical. Because I believe that these solutions will have a value in

combat casualty and in prehospital care. That is just my belief for a number of reasons. And then I would say, all right. I would just set some reasonable goal for a trial to demonstrate that it is not likely to kill patients, and just demonstrate that under controlled circumstances -- OR and emergency.

DR. GOULD: Yes. As a concept, that is all fine. But again -- I am going to sit down. But these are the numbers we have struggled with. So it sounds fine to say, but it is very hard to actually implement that until you actually look at the table.

DR. HOLCROFT: Well, I would say -- I would take the table as is. Maybe 500 to 1,000 patients in a group, which is not easy either I understand.

DR. GOULD: No, that is not easy.

DR. COHN: So, Jim, are you suggesting that the control arm have no blood available? Is that what you are saying?

DR. HOLCROFT: No. You see, no, you can't do that. That is the problem as I see it. I guess what I am saying is I would have a relatively -- I won't -- lax is the word that comes to mind, but that is not the word I want to use. But I just said it. But I would be relatively easy on the initial

trials in terms of showing equivalency. But I wouldn't use that for licensure. Rather, I would use that to design the trial that really counts, which would be the trial in which the only other option is to give normal saline. That would be the prehospital system. I think that is our problem right now. Unfortunately, we have the high death rate in the Baxter trial. If it weren't for that, probably most of us would feel -- at least I would feel comfortable entering patients into a prehospital trial if it weren't for the Baxter data. If I had just your data, you see, I would feel very comfortable entering patients into a trial. You gave 20 units of this stuff and you had 5 patients with hemoglobins of less than 3?

DR. GOULD: Less than 1.

DR. HOLCROFT: Less than 1 who survived. I have never seen a patient with a hemoglobin of 1 survive. I have never seen a -- I don't think I have ever seen a patient --

DR. COHN: Well, that is because you don't let your patients get down that low. You give them blood. I mean, you know --

DR. HOLCROFT: Well, no, not -- some of them I can't.

DR. COHN: This was not a random event

here.

DR. HOLCROFT: Unfortunately, I have had a few who have been down that low. I mean, if I just had those data, then I would say wow. Now it is time to go to the prehospital trial for the reasons I have mentioned.

DR. ALVING: Any other comments by the panel? Anyone willing to say what they will accept in terms of this 95 percent confidence interval?

DR. CARSON: Could I ask someone from the FDA to comment on the large simple style of clinical trial? Is that a sensible approach in this setting? You know, you are going to randomize these trauma cases, okay, with a 15 percent mortality. You are going to collect 3 or 4 pieces of paper on these people. You are going to get some baseline diseases. You are going to get some demographics. You are going to get some of their physiologic vitals and measures pre-randomization. You are going to measure their incidence of post-resuscitation mortality, which you can do fairly easily. You are going to measure their infarcts. You are going to do some of the obvious things like amylase and a few other very simple things, and you are going to limit it to just three or four pieces of paper. That is it. And I don't think -- you know, if you got rid of blinding

here -- I am not sure you should get rid of blinding, but if you could get rid of blinding, it would dramatically reduce the expense and increase the feasibility of the study. If you use mortality as your outcome, then blinding is not usually necessary, although there are some experiences with the Baxter trial that suggest that maybe that is not completely true. But I mean really take a very different approach than what is traditionally done. If you want to try to -- you know, these sample sizes are, to say the least, challenging. I mean, I want to see these drugs have a shot of getting approved, and I don't want to set the bar up to the level that it is impossible for anybody to reach. So this is one way of spending your money on a sample size and spending much less on data collection.

DR. WEISKOPF: I have one further perhaps question or comment to make, and that is we are basing -- and I think the FDA is -- I don't want to speak for them, but my sense is that they are basing a lot of this discussion based on the Baxter experience. And the question is whether all these other compounds that have been discussed this morning -- whether it is appropriate to apply the Baxter experience to those compounds. Are those other compounds likely to have the same risk profile as

based on the chemical composition and based on the pharmacology and clinical experience that is thus far exhibited, or are we applying too -- as you say, attempting to put the bar too high just based on the Baxter experience?

DR. FRATANTONI: Can I comment? We are actually at closing time. Perhaps I can just give the panel something to talk about at dinner and maybe give the FDA something to think about. A thought that I have been entertaining both before and after I retired from the FDA, and one that was stimulated again today by a discussion with Dr. Scott Swisher. Many of you know -- Dr. Swisher is in the audience somewhere -- he was the chairman of the Safety and Efficacy Panel of the FDA, which in the 1970's was charged with the job of determining whether or not all the approved blood products indeed had data to support their efficacy. Over the years, FDA has considered stronger emphasis on safety and less on efficacy -- periodically considered this. When you think about it, FDA gets in trouble when they do because of problems with safety. And in the current environment, given the scrutiny of medical services, it is unlikely that many products would be used in a frivolous manner.

Clinical trials are fun to design and

they are interesting to analyze, but they really don't reflect the real world very well. I think when we get misled occasionally, it is because of the artificial environment of the clinical trial, that things only really begin to show up when products are used in the real world.

So what I would propose for people to talk about is how would people feel about approving one or more products of the type we talked about today based primarily on safety data, which would be derived from a particular safety group and would therefore define an indication. To certainly require that there be demonstration of biological activity, which would at least show transport of oxygen, and that there be a supplement to this, a very carefully designed and rigorously managed post-marketing surveillance study?

DR. WEISKOPF: Joe, I think that is what I said at the last meeting that the FDA held when you were still working for the FDA -- when was that in 1995 or 1996? A long time ago. So, yes, I would be in favor of that.

DR. HOLCROFT: I'd be against it. Licensure is one thing. But if it is not going to save lives or improve neurologic outcome or have some other tangible benefit, I don't -- I can't see it.

At the same time, I do want to give the products a chance. So I would set a low bar for the initial evaluation of safety. That is what I am trying to say. And maybe I didn't say it clearly. I said a low bar. I would ask the company to enter 500 patients in either arm. And if it seems as if the mortality rate was not higher with some reasonable confidence in the patients who received the product, then I would go ahead and evaluate the product in a situation in which it had the chance of saving lives. And then I would set the bar high. Then I would say if this product doesn't save lives or improve neurologic outcome, then sorry. But if it does, then of course we are all fine. So I would put it in two stages is what I am saying.

UNIDENTIFIED PARTICIPANT: I would like to suggest a simpler model. Instead of trauma, where so many factors come into play, a simple model would be just simple hemorrhage. Let's say patients with a GI hemorrhage where hemoglobin drops to below 7 grams per deciliter. And let's pretend there is no blood available, and therefore we will use a blood substitute. In that case, we would see, focusing on a few parameters, would this blood substitute sustain tissue oxygenation. Maybe looking at different organs function. Would it prevent a multi-organ

failure? Would it sustain oxygenation? Would it sustain a lower lactate? And so on and so on. It would be a simpler model where hemorrhage would be the problem, rather than the interplay of hemorrhage plus broken bones plus a pneumothorax, and I will not mention head injury, where hemoglobin I think would be contraindicated. Would that be a simpler model?

DR. ALVING: It is a simple model. I think what the FDA would like to see, though, is a trial that would be conducted in the setting in which the product would actually be used, and trauma seems to be certainly a main target of the hemoglobin substitutes. And if equivalency at least could be shown in this setting, then it could move to the field, which again has great military interest. And also it could, I think, be extrapolated to be used for other kinds of patients in an in-hospital setting -- those with severe hemolytic anemia, those who are alloimmunized and really for whom there are no red cells immediately available. So this could be potentially a very great stepping off point. I must confess that although it is 1700 and already the FDA is giving me mixed signals, I feel like a manufacturer. One is saying this and the other one is saying that. I will always yield to the FDA. Please, one more comment, Paul, and then we will

close.

DR. AEBERSOLD: I just want to make a comment about exception from informed consent. The Agency recognized in promulgating that rule that not every trial would be a success. And there is a long-term commitment. There has been no talk that I have heard of of revoking the rule because of one trial. The ability to conduct a future trial with another blood substitute if exception from informed setting in an ambulance setting, for example -- as you mentioned, Dr. Holcroft -- depends upon the investigators and the IRBs much more than the FDA. And I think that depends on the data that the company has to present to you that their product, at least in your mind, would not have an adverse outcome and you would be willing to test it for a positive benefit, and the IRBs would have to agree with you.

DR. ALVING: I would like to thank the panel, I think, for a very stimulating discussion, because they represent not only lots of brain power, but different disciplines. And again, I would especially like to thank the manufacturers. We realize you spent years and years and millions of dollars, and I think your efforts will probably eventually be very fruitful. So thanks again for all of your complete cooperation.

(Whereupon, at 5:10 p.m., the meeting was concluded.)