U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

+ + + + +

PUBLIC HEALTH SERVICE

+ + + + +

FOOD AND DRUG ADMINISTRATION

+ + + + +

CENTER FOR BIOLOGICS EVALUATION & RESEARCH

+ + + + +

NATIONAL INSTITUTES OF HEALTH

+ + + + +

NATIONAL HEART, LUNG & BLOOD INSTITUTE

AND

UNITED STATES ARMY

+ + + + +

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

+ + + + +

TUESDAY, SEPTEMBER 28, 1999

+ + + + +

The Workshop took place in the Natcher Conference Center, NIH, Rockville, MD, at 8:00 a.m., Harvey Klein, M.D., and Michael Fitzpatrick, Ph.D., Chairpersons, presiding.

PRESENT:

HARVEY KLEIN, M.D., Chairperson

MICHAEL FITZPATRICK, Ph.D., Chairperson

JEFFREY L. CARSON, 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

MARGOT S. KRUSKALL, M.D., Panel Member

PAUL M. NESS, M.D., Panel Member

RICHARD B. WEISKOPF, M.D., Panel Member

GUS J. VLAHAKES, M.D., Panel Member

ALSO PRESENT:

ABDU ALAYASH, Ph.D.

PAUL AEBERSOLD, Ph.D.

TOBY SILVERMAN, M.D.

A-G-E-N-D-A

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

8:02 a.m.

CHAIRPERSON KLEIN: If I could ask the panelists to please take a seat at the front of the room. I've been told it's 8:00, and it's time that we get underway.

I'm Harvey Klein, from the Clinical Center here at the National Institutes of Health, and I understand that someone has absconded with the place tags and the names that we were using yesterday, so in starting this morning's session I'm going to ask each of the panelists to introduce himself or herself, so that our transcriber can identify them.

DR. HOLCROFT: I'm Jim Holcroft, from the University of California at Davis.

DR. WEISKOPF: Richard Weiskopf, University of California, San Francisco.

DR. KRUSKALL: I'm Margot Kruskall, from Beth Israel Deaconess in Boston.

DR. CARSON: Jeff Carson, from the Robert Wood Johnson Medical School.

DR. NESS: I'm Paul Ness, from Johns Hopkins in Baltimore.

DR. COHN: Steve Cohn, from the University of Miami.

DR. JOYNER: Mike Joyner, from the Mayo Clinic.

DR. VLAHAKES: Gus Vlahakes, Mass General Hospital, Boston.

CHAIRPERSON KLEIN: Thank you very much.

Now, our session has to do with the surgical issues, but I=m going to take the Chair=s prerogative in warming up this morning and start off with a question that=s a little different for the panelists here, and that is that we heard yesterday about the close linkage, at least the hope for a close linkage between preclinical studies and clinical studies for safety. What I=d like to ask the panelists is whether there are any consensus models that the FDA ought to be requiring? For example, we know that there=s the possum esophageal sphincter model, the rat mesentery, the dehydrated swine, the splenectomized fox hound, and hundreds of others. All of these compounds are a little different. In terms of moving from preclinical to clinical studies, are there models that ought to be compulsories that every compound should go through in order to say this is now ready for a clinical study?

DR. WEISKOPF: Let me begin by answering your question with a question, and that is, do we

really know as yet where the prominent toxicities lie for these compounds? Now, given we are dealing with at least two different classes of compounds, and within those classes the compounds vary, so there may be differing toxicities. For example, I was struck yesterday by some data that Doctor Saunders presented, but we haven=t had an opportunity to discuss, and that was that in one Baxter=s trials, perhaps, Mike might be able to comment on this, I=m not sure if this was overall or just one trial, Baxter noticed an increasing severity of stroke in the treatment arm, and is there an issue there? Do we need to have models that look at neurologic injury?

DR. COHN: Doctor Klein, I also have a question for you.

Are you asking this question for future products or for the existing products, because my understanding is that these products have gone through some acceptable preclinical evaluation and are now going through their Phase II and III.

CHAIRPERSON KLEIN: No, precisely, I am asking for future studies of future compounds, because, in fact, I think there=s some question in many people=s minds as to whether the appropriate preclinical studies were, in fact, done for some of the compounds that then

went into clinical studies.

DR. JOYNER: I think there are two issues here. One is, if you are trying to use them in a shock trauma resuscitation model, where typically people have assumed the potential patients are going to be reasonably young, reasonably otherwise healthy and so forth, although we heard yesterday that trauma is now -- the demography of trauma is changing, so I think that=s one issue.

The second issue is use in elective surgery, like in the hemodilution trials that people are talking about here, and I think the issue there is, in general, why do people die in the perioperative period? People don=t die from the surgery typically, they don=t die from the anesthesia, they die because something happens to their co-existing disease which causes a problem. And, if you look at who gets blood, and everybody here knows that 50 percent of the people who get blood are 65. The average person who has surgery at our place is like 62. And, these people, if you look at the Medicare database, you look at any database you want to talk about, these people, a high fraction of them have hypertension, a reasonable fraction have reduced ventricular function, a reasonable fraction have lung disease, a reasonable

fraction have either overt or covert renal disease and so on and so forth.

So, the thing is, if you want to use this stuff in elective surgery, ask yourself what causes problems in the perioperative period, and, again, in general it=s not the operation, in general it=s not the anesthesia, it=s some interaction of those things with the patient=s co-existing disease.

And so the thing that has struck me is, for example, the SHR rat, which has been a terrific model of hypertension or to follow up on what Doctor Weiskopf said the stroke-prone rats. Some of those models might be very helpful in trying to understand how these animals, especially a small animal model, how some of these compounds or future compounds interact with common co-existing disease.

For example, maybe these products would cause less hypertension or less relative hypertension in SHR rats because there=s some evidence that their nitric oxide system is already messed up and so you can=t inhibit something that already is kind of not there. So, there=s been some discussion about that.

So, to reiterate, one is, distinguish between whether you are trying to look at a resuscitation model or a resuscitation use versus an

elective surgery use. If you are going to do an elective surgery use, I think you have to start asking questions about co-existing disease that the patients are likely to have.

DR. HOLCROFT: In addition to all that, I=d make a vote for at least some studies in unanesthetized models. Of course, these products are going to be -- for this morning=s discussion -- are going to be used in anesthetized patients, so you might argue, what=s the point of studying the unanesthetized animal. But, at least in the shock studies, the anesthetized models and the unanesthetized models are different.

And then second, I=d make a plea for at least some studies in primates, and that=s just -- I guess it=s just a gut feeling, but I think we are kidding ourselves when -- let=s say it this way, it just seems that the primates are more like us than the others, and so if just ten or 20 baboons are thrown in there somewhere I think that=s worth it, and it=s not that much more expensive to do that.

DR. COHN: The other point, I think to make it clinically relevant we really need to focus on, in terms of the shock resuscitation models, really need to be uncontrolled hemorrhage rather than controlled hemorrhage, because I really don=t know how the

controlled hemorrhage model relates to the typical trauma patient who we are resuscitating at a time when they are still having, you know, a high degree of ongoing hemorrhage.

So, if we are going to devise the perfect model to mimic the clinical situation, Doctor Holcroft=s gut feeling may emanate from the fact that he does unanesthetized baboon research, or at least did, but I have to agree with him, I think that that would be ideal.

And, of course, some of our products have gone through that process.

DR. HOLCROFT: The controlled hemorrhage versus uncontrolled hemorrhage, I wouldn=t require all of the studies to be done in an uncontrolled hemorrhage model, just because those models are very tricky. You can pretty much, in our experience at least, we=ve been able to pretty much make uncontrolled hemorrhage models do anything we want.

The argument in the literature is whether in uncontrolled hemorrhage, resuscitation increases bleeding, and the literature is split right down the middle, and the people who think that it does have been able to, you know, design models where resuscitation does increase the bleeding, and those who think it

doesn=t have been able to devise models where it doesn=t.

So the advantage of the controlled hemorrhage model is that it is clear cut, everybody knows what you are dealing with, there=s a rich body of literature on it, and experience. The disadvantage of the controlled hemorrhage model, fixed volume model, is that it=s not realistic. So, I think both models have a place, but I wouldn=t restrict my research to just one of the two.

CHAIRPERSON KLEIN: Let me just push this a little bit further, if I might, and that is to ask those panel members who are willing to commit themselves, since you can change a model with almost any slight physiologic change that you wish, and make it do many different kinds of things, or show different kinds of things, or not show different kinds of things, would it be helpful to have three, or four, or five consensus models that every product is tested in before they go to clinicals? Well defined, well structured, all the conditions known, does anyone want to comment?

DR. HOLCROFT: Sure. I don=t think we could agree on that, I don=t think. We could try. I bet we can=t even agree here among the models.

DR. COHN: I agree that it would be hard to

get agreement.

DR. NESS: It would seem that one of the things that we=d want to do in selecting models for these situations would be to try to reproduce the toxicity that you think you=ve seen in the clinical studies or in some of the other animal models. For example, the neurotoxicity, infectious complications, those things.

I=m kind of concerned that unless we try to understand what causes them in these toxicities, if they exist in early studies, we=re going to sort of be plagued forever, you know, showing that they don=t exist in humans, and the field is never going to move ahead.

So, for example, the neurotoxicity which seems to be an issue, it would seem to me to be very important to try to understand mechanistically in some way why this seems to be occurring. Is it a vasoconstrictive event, is it a direct toxicity, what is it, so that one can then study it in models, study it in patients, and either say this is real, we need to deal with it, or it=s not real and we don=t have to worry about it in licensure studies.

CHAIRPERSON KLEIN: Any other comments?

Doctor Kruskall?

DR. KRUSKALL: I think it would also be worth thinking about rechallenge experiments. I=m trying to think of the ways in which any of these products could be used once they=ve been licensed for one indication, and I envision scenarios where patients are given this material over a longer period of time than just in an immediate surgical setting, or are rechallenged with the material some weeks or months afterwards. And I=d like to understand in an animal model whether there are additive or anamnestic effects to the substance.

DR. JOYNER: I think it would be ideal if you could have three or four common models. Again, it would be difficult to agree on them, and part of that goes to whether you are thinking about this in terms of a resuscitation fluid or use for an elective surgery to spare blood.

I think it would take some time, but I think if you came with three or four, or if the FDA perhaps gave people kind of a Chinese menu approach, and said that there were six or eight acceptable models, and depending on what those folks, what indication that they were aiming toward, whether it=s like the Alliance folks who are looking more for the hemodilution approach, versus Doctor Gould=s group,

which is looking more for volume resuscitation, they may pick three or four of the six or eight, and that way you would ensure there would be some overlap between one or two, so maybe four out of six. So everybody would have two in common, and there would be some overlap, and then the people would be able to have specific models if they are not going to be using it in volume resuscitation maybe, or don=t want it licensed for that, maybe it wouldn=t be as necessary to do one of these uncontrolled hemorrhage models.

CHAIRPERSON KLEIN: Yes, another comment?

DR. COHN: I don=t know, it bothers me that we are going to force industry to comply with -- to use a set of models which are just as arbitrary as any they might choose. You know, I think it=s one thing to say we have a model, we know that this is the right model, it=s been validated for the use, you know, we don=t have that, and we could get a group of panelists together here to talk about hemorrhagic shock, and we would all agree on what we don=t know, but I=m not sure that we could all agree on what the perfect model was on whatever subset of patients you want to look at.

So, I think -- I happen to know that the Baxter product, for example, had gone through some of the kinds of testing, top off, top load, repeat,

studies that we=re talking about. They also did a series of studies in shock models, showing that it was actually beneficial in the setting where parts of the cerebral circulation were occluded. So, I mean, it just underscores that while some people are pigs, all pigs are not people, and that, you know, you can=t generalize from an animal model without actually looking at it in -- yes, you can, you know, I=m not sure you can generalize.

So, I mean, probably whatever industry does has to meet some level of acceptability at the FDA, and the FDA may change its opinion, you know, over a period of five or six years, which happens. I would hate to tell them that these are the three or four perfect models and you have to all go through them, so they all go back to the drawing board, prove it in those models, and then the FDA changes its opinion and now those models are no longer acceptable, because our knowledge scientifically is changing. What used to be a perfectly acceptable Ringer=s model 20 years ago is now felt to be, well, it=s nice to go from the uncontrolled to a controlled -- a controlled to an uncontrolled model in the setting of shock.

So, I think our understanding is in evolution, it=s hard to, you know, lay down the Ten

Commandments here.

CHAIRPERSON KLEIN: And, all people are not pigs, I guess, is the final.

I=d like to go back to one other safety question before we go back to elective surgery, and that is, under safety question number one we have the question, are there other potential toxicities in addition to the ones listed in the first paragraph that you think should be added to this list? And I=d also like to ask the panel a corollary to that, and that is, we frequently hear, well, there is neurotoxicity, show us some studies that tell us your compound doesn=t have neurotoxicity, or doesn=t generate free radicals. Do you have any specific recommendations on how to look for some of the clinically relevant toxicities mentioned in this first paragraph or not mentioned in the first paragraph?

DR. HOLCROFT: In an animal model, Doctor Klein, or clinically?

CHAIRPERSON KLEIN: Either one.

DR. HOLCROFT: Animal models, I wouldn=t know how to do it, but the clinical question is easy. You just look at Glasgow outcome scales, scale scores. So, that=s straightforward.

The animals, I wouldn=t know how to do.

DR. CARSON: Harvey, what are the neurotoxicities that have been described?

CHAIRPERSON KLEIN: There are a variety of neurotoxicities described in vitro, and we just heard about the possibility of stroke being one that=s actually not on this list in specific, but may be a very important one. And, I guess the question is, is there -- are there specific assays that would help predict these, either in the preclinical setting or that ought to be looked at specifically in the clinical setting?

DR. VLAHAKES: This is a hard one, because a lot of these things are going to be dependent on the substrate you are starting with, namely, pre-existing conditions, many of which may be undiagnosed like small vessel cerebral vascular disease. And, for example, if hypothetically a material caused thrombosis to occur in small, diseased vessels you are not going to really be able to make a preclinical decision based on studies of the coagulation system or studies of rheology. Rheologic studies would predict, for example, that adding oxygen content and diminishing the viscosity of the blood favors oxygen delivery. So, the ultimate studies are going to come out of Phase I and the extension into patients in Phase II.

The safety data accumulated in Phase II trials with this class of materials at this stage of the development, I think is key.

DR. WEISKOPF: In addition to what is labeled here as cardiovascular/hemodynamic changes, I would add the possibility of direct myocardial injury. There are a number of preclinical studies, I think, from various of the hemoglobin based compounds that have noted some myocardial issues in various animal models, and I think we heard yesterday that at least one of the studies noted an incidence of myocardial ischemia.

CHAIRPERSON KLEIN: Are there specific assays that you would recommend, or anyone else on the panel?

DR. JOYNER: In all the data I=ve seen with this generation that=s been published, people have been quite rigorous I think in looking at some renal issues, and I=m surprised that renal toxicity isn=t there. I think that the class of compounds that have been talked about now have done a good job trying to demonstrate in animal models that those issues are not huge, but certainly everybody is aware of the potential impact of hemoglobin on the kidneys. And so, I think that should continue to be monitored closely.

DR. KRUSKALL: I would agree with that, and it would seem to me that we ought to require careful studies of kidney, liver, pancreatic and perhaps muscle injury as well, in terms of the endpoints that are looked at, both in animal studies and in human studies. I don=t want to see those brushed under the rug, as enzyme changes of unclear significance. I think they have a real phenomenological meaning we have to understand.

CHAIRPERSON KLEIN: Dick.

DR. WEISKOPF: One further comment. I think most, if perhaps not all of these, are addressing hemoglobin-based compounds, but, again, we are talking about at least two different classes of compounds, whereas these may apply to the hemoglobin-based. Are there issues and toxicity issues that we need to address for the fluorocarbons?

PARTICIPANT: (Speaker speaking from an unmiked location)

DR. WEISKOPF: Sorry, I was only reading the first paragraph.

CHAIRPERSON KLEIN: Doctor Ness?

DR. NESS: Yes. We heard yesterday, for example, of some preclinical stuff, or even first phase stuff, where patients were being infused while awake,

and had nausea, vomiting, GI upset, fever. It would seem to me that those are potentially important signals of something that may actually get worse in patients who are stressed receiving these compounds in surgery, or in trauma, or whatever else we would choose to do with them. And, therefore, at the very least I think we would want to know, what is the mechanism behind these toxicities or symptoms that these patients, healthy subjects, are encountering? Can they be pharmacologically blocked? Are they the sort of harbinger of something more serious? It seemed to me that we were being a little casual about some of these sort of side effects in healthy subjects, which could be potentially dangerous.

CHAIRPERSON KLEIN: Does anyone want to comment on specific methods of detecting some of the generic toxicities, renal toxicity, neurotoxicity, free radical generation, or any of the others that are listed in paragraph one?

DR. JOYNER: I mean, I keep -- I hate to keep beating a dead horse, but I think that looking at these models of co-existing disease would be reasonable in animal models, for hypertension. It would be reasonable to look at some of the cardiovascular issues, and also with the animal model of reduced renal

function. I think those are essential, because whether you are talking about trauma or using elective surgery, again, in elective surgery, especially in older patients, in some cases a majority, but certainly a lot, in all cases those folks are going to have compromised renal function and hypertension.

DR. COHN: I think without naming a specific test, I think that the last thing there, decreased host resistance to overwhelming infection, and specifically multi-organ failure, would be a very important thing to follow in these patients, honestly not so much, or as much for the new product, experimental product, as for blood itself.

One thing I don=t think we=ve talked about much at this symposium is the immune-suppressive effects of blood itself, and that one of the potential benefits of the blood substitutes is that they may have a much less immune-suppressive effect. So, that may be, while maybe mortality is equivalent in the two resuscitation arms, that it may be beneficial to use the new products in terms of their immune-suppressive effect. So, I think it=s important to evaluate that and, you know, look at a whole variety of different areas there.

Recently, there was a paper presented where

they looked at neutrophil priming in the PolyHeme resuscitated patients versus patients receiving blood in the setting of trauma, and they found that the ones that received PolyHeme actually had a markedly diminished neutrophil priming as evidenced by CD11b, super oxide anion and elastase. So, I mean, the neutrophil priming was diminished in the humans, the patients I should say, who received the blood substitute, and I think that may be a potential benefit. So, I certainly would, while I think we certainly need to follow safety issues, there may be some potential benefits that could be uncovered by closely monitoring their multi-organ failure and their incidence of overwhelming infections.

CHAIRPERSON KLEIN: If there are no other comments on this issue, let=s move to the item three, which is elective surgery, and is the topic for this morning=s first panel, and we can start right on with question A, shouldn=t oxygen therapeutic be evaluated in a controlled clinical trial in hemodynamically unstable patients requiring blood prior to licensure for elective surgery, to ensure that its use in surgical patients at the highest risk would not lead to a worse outcome than if blood were used?

Anyone.

DR. VLAHAKES: Can you tell us what you mean by hemodynamically unstable, at least the degree.

CHAIRPERSON KLEIN: Well, I=m going to ask about the gamut of patients, clearly not the patient that=s totally elective that comes in for their bypass.

DR. WEISKOPF: Well, this says, the title here says elective surgery, so now you are talking about a hemodynamically unstable patient undergoing elective surgery. I=m not sure how you would do a study like that. That means either you select somebody who is going for elective surgery who was hemodynamically unstable prior to elective surgery, that=s difficult to comprehend, that it=s actually truly elective, if the patient is hemodynamically unstable.

DR. SILVERMAN: Toby Silverman. Let=s make it simple, let=s call it perioperative use rather than elective surgery.

CHAIRPERSON KLEIN: Toby, just one clarification, do you mean for the unstable patient perioperative use as sort of a worst case scenario, before you would take such a compound into the strictly elective surgery stable patient venue?

DR. SILVERMAN: Right. If you take a look at the rest of the questions, one of the questions has to do with when you study someone undergoing orthopedic

surgery, we want a broad distinction between unstable patients and a stable population.

DR. JOYNER: But, in general, people that have orthopedic surgery, it=s truly elective, and they are worked up and they have their echo, and they go to see the cardiologist and they are about as tuned up as they can get, some have angioplasty beforehand, or they are people that have long bone fractures and are done on an urgent or emergent basis. I mean, so there=s -- I mean, I think Doctor Weiskopf is saying that an unstable elective patient is kind of a contradiction in terms. Either the patient is stable and it=s elective, or there=s an urgency where we can=t work the system out.

DR. SILVERMAN: Let=s just change the title to perioperative use outside of the trauma setting.

DR. VLAHAKES: Well, there=s two kinds -- to try to take this down one road or the other -- there are two general types of clinical scenarios that might come up in a perioperative setting. Number one, the patient who is euvolemic, who has received, let=s say, crystalloid or non-heme, non-oxygen-carrying colloid replacement, and who has become anemic, typically it will be, for example, the cardiac surgery patient who has been rewarming in the ICU and is getting fluid

repletion.

So, you have a euvolemic, stable, perioperative patient for whom you are going to treat anemia, for concerns about oxygen carrying capacity, perhaps the SVR is low, versus a patient, on the other hand, who might be hypovolemic from blood loss in the operating room.

So, if I can give a definition to what=s written in the document, let=s say that unstable means the patient who is hypovolemic because of surgical blood loss that is occurring at the time the decision needs to be made to infuse and let=s work from there. Those are two different scenarios, number one. Number two, they may have different -- they may have different implications for a safety profile. They also have different implications for the range of data that you could collect because of the rapidity with which transients may occur. And, I think they have to be designed differently in clinical trials.

DR. WEISKOPF: Well, as any clinician in the room knows, those of us who work in this environment have a goal of preventing somebody from becoming unstable. And so, and transfusions are ordinarily given, not to somebody, except in a trauma setting, not to somebody who is unstable, but because of acute

anemia or ongoing blood loss, but not to the degree that makes the patient unstable.

If one seeks, for whatever reason, to produce a study in somebody who is Aunstable≅ in the perioperative period, it=s difficult to imagine a satisfactory design of such a study where those patients can be adequately captured in an appropriate time period, that to gather an end that would satisfy, I think, regulatory authorities to be sufficiently powered to catch whatever safety issues one is looking for in this population, I think would be exceedingly difficult.

DR. COHN: I would add to that by saying that the kinds of patients you are talking about are, you know, I mean you could come up with a couple of different categories, liver transplantation, massive upper GI bleeding requiring gastrectomy, massive lower GI, I mean there are a number of different situations where a patient is having ongoing hemorrhage in the elective or semi-emergent situation. There=s a whole lot of background noise in those patients. I think it would be very difficult to separate out the fact that the guy has got underlying cardiac disease, is on anticoagulation for his valve, and has developed an upper GI bleed where a normal person would have

responded to endoscopy, you know, or endoscopic cauterization. I think we are looking at a complex group of patients who become unstable. I don=t think it=s the routine patient, and I think it would be very difficult to separate out all the underlying things that led to them becoming unstable. I think it would be a very difficult thing to dissect out the impact -- safety issues that might come along with a new product. I think it would be very hard, even harder than trauma.

DR. VLAHAKES: Let me expand on that by putting a suggestion on the table. New class of products, not a tremendous clinical experience out in the field, and you also, not only from the standpoint of the FDA, but also from the standpoint of people interested in using these materials, and certainly from the standpoint of companies, would like to have, number one, the safest environment to ensure success in the regulatory process, but secondly, the best opportunity to gather data, which is desperately needed with something that is very new, and the best opportunity to detect an adverse occurrence, and to understand it, so that it can be, you know, fixed or done away in future materials.

I would urge that this, for initial

clinical trials in this setting, that we consider using the euvolemic patient who is anemic, where materials are being given for their oxygen carrying capacity, and you have the best opportunity to gather data that=s not going to be confounded by other transients that are occurring.

DR. HOLCROFT: I=d vote on that, too. I would think it would be easier and overall better to start out in a controlled situation, with a patient who is fully monitored and so on. And, I think you are more likely to get good safety information, at least initially, on those patients, and then take it to the more complex hemodynamically unstable patients.

DR. VLAHAKES: That would include postoperative anemia, and it could include --

DR. HOLCROFT: Yes, sure.

DR. VLAHAKES: -- the ANH, the acute autologous donation protocol that was described.

DR. HOLCROFT: It would include any of those, and then a very careful look at things like enzyme changes and so on.

DR. JOYNER: I would like to echo what Doctor Weiskopf said. As anesthesiologists, we spend a great deal of time and effort making sure that patients don=t become unstable. Most of the -- I don=t know, I

always thought that most of the transfusions that we give, in fact, are preemptive. We give them before the patients become unstable, based on the type of operation the patient is having, our estimates of ongoing blood loss, the fact that we can monitor patients, maybe we have their hemoglobin and so forth.

The second thing is, is if you think about operations like liver resections, Whipple procedure, and so forth, we do a lot of those in Rochester, and the patients are all treated as if they are going to have, you know, massive interop hemorrhages, and very few do, but we are there with, you know, blood in the room and so forth for the three, or four, five, or ten percent who need it, but the rest of the people just kind of sail through and maybe get one unit, maybe get two units, a lot of them get none.

And so, a lot of what we do, at least in the ORs and in anesthesia, is preemptive, and our goal is exactly what Doctor Weiskopf said, it=s to never have anybody get unstable, never have anybody get close to unstable.

And, at big centers, in large part, people are quite successful doing that in very sick patients having very big operations electively. It=s not as dramatic as people think.

DR. KRUSKALL: So, rather than the unstable patient, I=d actually prefer to see the stable situation, but I=d like to ensure that it=s pushed to its extreme. It would be frustrating and not a guarantee of safety if the typical hemodilution that many people use or envision doing comprise the majority of this trial, in other words, a two or three unit dilution. I=d like to see us push and define the extremes and ensure that those are included for at least some of these patients. So, for example, getting down to hemoglobins of five or so.

DR. NESS: Yes. There are a couple of -- we certainly could do a lot of elective surgery and hemodilution stuff and find out, perhaps, what the safety profile in patients, whether we=ll really learn very much about efficacy under those situations, in terms of really doing anything for the patient, is unclear. But, there are, I think, a couple of sort of elective surgery situations where there is high blood volume used, that the patients, I=m sure, become hypovolemic, and these go on in big centers in things like thoraco-abdominal aneurysms. We seem to do one every Wednesday, and a couple of coolers of blood go up there for about 30 units each case. These are electives. The patients are studied pretty extensively

beforehand. I think there are a number of centers who are dealing with these types of cases, and I think it is reasonably controlled. Liver transplant, obviously, because of liver failure up front, makes it a much more complicated case to study, but there are some very large cardiac or vascular cases that could be studied which might put more stretch into these studies.

DR. JOYNER: Instrumented backs, too.

DR. WEISKOPF: Sure, and I=m sure some of the sponsors are investigating their compound in those sorts of patients, but large blood loss does not necessarily mean an unstable patient. One can maintain stability despite an enormous amount of blood loss, excluding the trauma circumstances that we were talking about yesterday.

CHAIRPERSON KLEIN: Doctor Carson, you had a comment?

DR. CARSON: I think it would be desirable to try to deal with the hemodynamically unstable patients if you could, but I think trying to generate the kinds of numbers and logistics of implementing a protocol like that probably makes it unlikely to be successful.

So, I support the general consensus that I=m hearing, which is that you are going to need to do

this in a more routine, oriented type of patient, recognizing that there will be a component of those cases who turn out to be hemodynamically unstable, and there=s a lot going on with them, you know, and you can stratify your analysis in that group. And, if you have a big enough number then you may have reasonable numbers of patients to look at.

It may turn out that your trauma model really is your best model to try to look at the hemodynamically unstable patients, and that trying to do it in a more general surgical environment probably you are not going to have the ability to do that.

DR. AEBERSOLD: Paul Aebersold, FDA. I think your point is well taken on trauma and, perhaps, one way of rewording this question would be to say, should these products be evaluated both in the surgical setting and in the trauma setting independently, two different types of trials, rather than just surgery alone.

DR. CARSON: I would think that would be highly desirable, because I think that the volumes of this drug that are going to be given in two settings would be completely different, I suspect. You know, what are the implications of the hemodynamic changes that are occurring in a trauma setting, and does that

change the way these patients tolerate these drugs? You know, is the stress of that environment going to bring out adverse effects that you won=t see in other settings?

So, I think it would be desirable to do it that way, if you could.

DR. WEISKOPF: I=ll disagree with that. I think as highlighted by the study we saw from Baxter yesterday, trauma patients are not a homogeneous, normally distributed population. You cannot -- I don=t think one can ever expect to get a reasonably matched group, a control versus treated arms, given the diversity of injury that can occur, and the difference in duration of time until patients get to the site of treatment. The pathology is just so diverse that I=m not sure what information one ever will get out of that kind of study. I think that was highlighted by some of the information that we heard yesterday from Doctor Saunders, and if a manufacturer decides they don=t want to have a trauma indication, is it our place to force them to do that?

DR. CARSON: If you have a large enough study these things will randomize out and the heterogeneity will be distributed equally.

I agree that you will wind up with probably

a pretty heterogeneous population, and, therefore, it may be harder to isolate the effect of your intervention from background noise, which is what I think you are saying. But, the adverse experience that occurred in the Baxter trial, if you had enough numbers, and you had central randomization, you conceal randomization, that if you had reasonable numbers those things will fall out and will be equally distributed among the two groups.

I=m not sure about, you know, how important the fact that you have very different patients and how these people have many different problems, whether that will make it possible to figure out what=s going on. But, if the common theme is hemodynamic instability, and you are replacing, you are giving them one of these new drugs compared to giving them allogeneic blood, I think you should be able to look at that question and see whether these drugs seem to behave and do the things that we want them to.

DR. WEISKOPF: Without wanting to press the point beyond reason, whereas, hemodynamically certainly the products are being tested in trauma setting for hemodynamic instability and for oxygen carrying, that is not necessarily the overriding issue that is the pathology for that given patient. They may have

important bleeding and simultaneously have an injury that is equally as important or even more important, for example, as closed head injury. And, we all know there will be a certain percentage of patients that will not have that closed head injury determined at the time of treatment, or initiation of treatment, and there are other things that go on as well. So, I think these are important confounders that I don=t think can be made to be equivalent at the end of the study, even with a large "n".

DR. KRUSKALL: But, I'll weigh in also, I mean to the extent that we are considering these oxygen carriers, and the subtlety that we are trying to forget, but the users won=t, is that these are blood substitutes, I think that there will be a temptation to want to use these in situations beyond elective surgery.

And so, I think relying on statistics in a well-designed trial to help us appreciate the confounders, to me the trauma situation is essential for understanding the extremes in which a blood substitute could create a problem where the use of blood would not, and I would want to see that done, even in a substitute that was being proposed only for elective surgery, just because one knows the limits

would be pushed beyond the very stable patients for whom this was originally designed.

DR. CARSON: One other thing is, and then I=ll stop arguing, if you look at the A Baer trial, the TRICK trial in the New England Journal in February this year, that=s an ICU trial and, in fact, it=s a very heterogeneous group of patients. They are surgical patients and medical cases. You know, they are sick as hell, like most ICU patients in North America, so I don=t know that it=s that dissimilar a situation to the trauma.

I think the head injury issue, I agree with you that it seems unlikely that blood is going to influence the outcome in relation to the head injuries, and so you are going to have to think about strategies to keep those cases out of the trial. And, if they get in the trial, then what that means is you are basically getting subjects who are not going to contribute information to the question you are trying to answer, because it=s not likely that blood will influence neurologic outcome in, you know, someone who has an intra-cerebral hemorrhage, or, you know, some awful neurologic event.

DR. KRUSKALL: But, that=s just as true at the other end. I mean, there are many patients who are

going to be studied in elective surgery whose outcomes are going to be independent of the use of the blood substitute, and we are not throwing them out. We are just taking them as part of the study.

DR. CARSON: Oh, I=m not suggesting you throw them out. I think when you think about your power, it just means that you are going to have subjects that are probably not going to contribute to the information you are seeking. So, you know, it makes it that much more challenging, you=ve got to crank up the numbers even further.

DR. WEISKOPF: I think I=m beginning to hear support for what I said yesterday, that death is not a sufficiently sensitive outcome, and not necessarily appropriate for the thing that=s being studied.

DR. COHN: But, it would have to be shown to be equivalent. It may not be, you may determine that it=s not your only endpoint, or even what turns out to be the most important endpoint, but it=s a key endpoint. I think it would be number one on my list. I just want to make a comment about, at the risk of, you know, the old proverb, you know, if you are a hammer the whole world looks like a nail, I think that if we don=t do a trauma trial somewhere along the way here, that an area where there is very likely to have a

great use of the blood substitute is going to be inadequately studied, i.e., I think that we are going to use these blood substitutes as a bridge in situations where we have uncontrolled hemorrhage. I mean, I don=t see this as, you know, going to replace blood in the setting of cardiac surgery in a patient who has inadequate circulating hemoglobin. Okay.

In fact, even in the early PolyHeme trial, I keep coming back to that, where they did not find a difference at 48 hours in the amount of blood transfused. Well, I mean, it may be that we have to give the blood later, but one potential major benefit of this would be as a bridge, the liver transplant that goes bad and needs 100 units of blood now, may get 99 units of a blood substitute and the next day get ten units of blood. So, we probably ought to look at it in the uncontrolled hemorrhage situation at some point, maybe to get licensure the FDA will determine that we=ll do a controlled, you know, orthopedic back trial or something like that, or a coronary bypass trial. But, I would think we would be somewhat uncomfortable about, you know, feeling it was acceptable when the chief use of this may well be as a bridge in a variety of situations that are very difficult to study, but, nevertheless, that=s where it probably will be used.

DR. HOLCROFT: The point has already been made by the panel at the other end earlier on, but I=d like to -- maybe I should just state my biases right up front, and then I=ll tell you why I=m going to say what I=m going to say.

I=m skeptical that using these substitutes in the elective surgical cases is going to prove to be that much benefit. The facts are, as Doctor Klein pointed out yesterday, we have an extremely good product now, it=s very safe, one in a million chance of getting AIDS, one in a 100,000 or so of getting hepatitis, and even if you get the hepatitis the chance of its killing you is not that high. So, we have a real good product now that can be used in elective surgery.

The only reason for giving a substitute would be to somehow avoid using this extremely good product that=s already available, and somehow keep the -- just keep everything pure so the patient only receives his or her own blood. The potential benefit there I think is minor. Now, there might be something to it, I may be wrong, and I=d be happy to be proved wrong, but that=s my bias right now.

On the other hand, I can see some of these compounds being extremely useful in the combat casualty

area and in pre-hospital care of trauma patients. I could easily imagine these products savings lives and saving neurologic function. I think that requires no stretch whatsoever of my imagination.

Okay. Now, if that=s case if you start with that bias, and I do, at least until, you know, I can hear some more, then it seems to me that the way you=ve got to do the studies is that first of all you have to have some assurance that the products are safe, because only then can an investigator in good conscience carry out a study in which no permission is going to be obtained from the patients.

So the next step is to see if it=s safe, and that=s why I think this question is so critical, because the question reads in IIIa, what should be done first, elective surgery or trauma surgery? That=s kind of what it is saying. And then I would say, well, actually for safety purposes the elective situation is where you can get the really good data, even though I doubt very much if it=s going to -- if these products are going to be effective, or better than what we now have.

So I would vote for purposes of getting to the trauma trials, which is what I think we need, I would propose my answer to that question would be, do

the studies in the elective case, especially for those who believe that, indeed, there might be some benefit to the patients in the elective case, then from these elective patients you should get an idea of how safe the compounds are, at least safe enough so an investigator could use them in a setting without informed consent, with the understanding that it may well be that there will be complications in the unstable patient, in a trial patient, that didn=t show up in the elective cases. I=d be more than willing to accept that concept, that it=s true.

On the other hand, in the trial cases there=s also the chance that you can really benefit a patient, and then that will come out in the mortality data or in other endpoints like neurologic outcome.

So, my vote would be, I=d like to see the safety trials done under the elective setting, so that we can get on with the trials that I think are going to really count.

DR. CARSON: I think that=s a well-reasoned argument, but it all hinges on whether you are comfortable sending patients -- whether you are comfortable entering patients into a trauma trial without consent, because, ultimately, I think you are largely going to have a hard time doing it in many

situations.

And, you know, I=m not sure that I know or understand the ethical part of this thing as well, because, see, I think you are right that the best chance for these drugs to truly impact outcome is in that setting. So, in essence, what you are saying is that we=re going to wait to study the setting where we have the greatest potential to improve outcome to try to establish safety first, and so it has the disadvantage of delaying the evaluation in the place that it could have its biggest outcome. But I think it=s a well-reasoned argument.

DR. HOLCROFT: With respect to entering a patient into a trial without permission, or without consent, you see, patients who have a systolic pressure of 89 or less in the field, I=m talking about blunt trauma patients now, and a Glasgow coma scale score of eight or less, have something like an 85 percent chance of dying. Those are the facts.

So, I=d figure, all right, 85 percent chance of dying --- oh, and you can=t do too much worse than that, so I=m more than willing to try something to try to save some of those lives. We have evidence that it=s possible to do that with other modes of resuscitation.

DR. CARSON: Jim, you=ve just convinced me that you should do that trial and not wait for the safety data, because, I mean, how much worse are these folks going to do even if these drugs cause trouble?

DR. HOLCROFT: Well, on that one -- well, I think that=s the way Baxter trial should have been designed actually, but I wasn=t asked. But, I think -- and there are patients out there, and not only is it death, but it=s morbidity, these are patients who end up permanently impaired, and a tremendous burden to themselves and to their families, and to society. Nonetheless, I think you need to pick those patients to do -- eventually that=s -- I think you can justify doing studies without informed consent if you pick patients who really have a pretty dismal prognosis, and that=s a problem I=m going to have with the elective surgery, you see, because elective surgery the facts are, even doing thoraco-abdominal aneurysms, which I do just about Tuesday in our place, the facts are is that the great majority of those patients do fine, thanks to our anesthesiologists who keep them from crashing.

But, the patients with the head injuries, and the hypotension, they don=t do well.

CHAIRPERSON KLEIN: I think you may have in part already answered the second part of this question.

If we take the definition of unstable out of the mix, and say, if we are going to do elective surgery for safety, should we select a population that=s relatively high-risk rather than a population that=s relatively low risk, and, if so, what is that population?

DR. HOLCROFT: We=ve named some of the high risks, thoraco-abdominal aneurysms, that=s a high risk, liver transplants, that=s high risk, I think we=ve named it, we do cardiac surgery maybe, I=m not sure, so we can tell you the high-risk procedures, that=s no problem.

DR. VLAHAKES: Those settings also have the advantage that the patients tend to be very well instrumented, and, again, I think this entire endeavor is in a relatively young phase compared to other things that are out there in the pharmaceutical world, and getting the data, accumulating a database, not only for the vendor, but also just for the regulatory process and for the field, is important.

So I echo that using those sort of big operation-type patients where you have the instrumentation and the follow up, the patients tend to be a little bit more well characterized in terms of co-morbidities.

DR. WEISKOPF: Let me get around this

question for a moment, and that is in order to show efficacy for any of these compounds that we=ve been hearing about for the past day and a half, for interoperative elective surgery there must be a substantial amount of blood loss. That makes all those patients high-risk patients by the nature of the operation that=s going on, and by the nature of blood loss. So I think these are being done in high-risk patients to begin with.

Now, if you are talking about some additional co-existing disease preoperatively, that=s a separate issue.

DR. JOYNER: I agree with that comment, and if you think about using them in orthopedic patients, orthopedic surgery may not be risky, but the patients are old.

So, when you start getting a cohort of people that are 65 or 70, they are all going to be -- there=s two types of risk here, high risk for bleeding and then high risk for -- they=ll all have co-existing disease, and high risk for perioperative problems that would be associated primarily with their co-existing disease.

So, I think that you can=t get around it. And, there are a lot of really -- I mean, people don=t

realize this, there=s a lot of really sick people having hip replacements, people with 25 and 30 percent ejection fractions, COPD, bad COPD, diabetics and so forth. They are stable and they are Amedically tuned up,≅ but it happens all the time.

I mean, Doctor Weiskopf has been at it longer than I have, but the thing people have to realize is that we routinely put, or anesthetize, sometimes it=s regional anesthesia, do this to really very sick people, and almost nothing ever happens. It=s boring down there. I mean, it=s boring, I don=t know how it is at your place, but there=s weeks that go by in the hallway where I work where there=s 14 operating rooms and about 16,000 cases a year, I mean occasionally it=s a nine-ring circus, but there=s weeks that go by that nothing really very interesting happens. The cases get put on, they get taken off, and, you know, there=s no codes, nothing. I mean, it=s just --

DR. CARSON: We really feel bad for you.

DR. JOYNER: No, it just goes along. And, you know, I mean, what is it, it=s 99 percent boredom and one percent terror, and when something happens you have to be able to respond, but there=s a lot of weeks where nothing happens.

CHAIRPERSON KLEIN: I think we are all gratified to hear that, actually, since most of us are asleep when we are exposed to this.

But, I guess the point is, in that setting, especially with the potential co-morbidities that you mentioned, perhaps then that might be an ideal setting to look for toxicities of these compounds, as you said, even though there are co-morbidities, and they are elderly patients with a variety of disorders, generally things go reasonably well. If they don=t, then we ought to be able to see that fairly easily against the noise background and, perhaps, that answers some of Doctor Kruskall=s issues with trying to push the system, is that sufficient to push the system?

DR. KRUSKALL: Yes, I=m wondering, and I need help as much from the panel as from the members of the FDA, as to whether we still haven=t covered the situations where we might find ourselves using blood substitutes, for example, in an older patient with renal failure, or the patient undergoing surgery who has chronic liver disease, is it sufficient to let the role of the dice get us these patients through elective surgery, or through situations of trauma, or would it be necessary and valuable to insist that some of these infusions be done in patients with decreased creatinine

clearances, or with chronic hepatitis, viral hepatitis, or other hepatic abnormalities?

DR. VLAHAKES: Those have been exclusion criteria of clinical trials in the past. The question is, looking at it from the company=s standpoint, the doctor=s standpoint, and the regulatory standpoint, when do you cross the river Styx with respect to those kind, particularly hepatic and renal insufficiency, you know, and I don=t know the regulatory process to know how you do that, or what the recommendations are, or is that something done after market approval in simple kinds of patients, and I=d be interested in what folks from the agency have to say about that.

DR. SILVERMAN: Toby Silverman, FDA. We have recommended that all patients cleared for the surgical procedure be eligible for enrollment. We have not mandated that particular groups of patients at these high risks be enrolled, but we have asked that all patients cleared for the procedure, for just the reasons you are talking about, be eligible.

DR. CARSON: Traditionally, when you look at trials for new compounds, these kinds of patients are always excluded from these trials, and I would urge that the FDA require these patients, that you take a consecutive group of patients, and unless there=s a

clear contra-indication to drug that they be enrolled in the trial, and that the sick ones not be allowed out of the trial, so that you can get this information.

Traditionally, in the evaluation of drugs, these patients are not there, therefore, the population that regulatory approval is based upon are the patients that are the healthiest and, therefore, the least likely to find the adverse effects we are worried about.

And so, if we require them, then we are more likely to learn about this in the pre-marketing phase of this evaluation.

DR. SILVERMAN: Again, Toby Silverman, FDA. By saying that all patients cleared for the procedure are eligible, and by saying that patients may not be excluded by whim of the investigator, I think that we=ve gone a long way to including the patients that we=re most interested in seeing here.

We=ve recommended that specific exclusion criteria for liver disease and renal disease be removed. We=ve really limited the exclusions for these clinical trials. So we are trying to get all comers here.

DR. WEISKOPF: Well, I think that=s a reasonable approach. On the other hand, I think, at

least in the elective surgery environment, one is unlikely to accumulate very many of those patients. If one takes electively cases that are going -- that have substantial blood loss, which is what the studies are going to be in elective surgery, in order to show some sort of efficacy, by and large those patients will not have substantial renal disease or exceedingly important pulmonary disease, because, remember, it=s elective surgery and they will have been excluded by the surgeon as not appropriate for this type of surgery.

So, whereas, I think that=s the appropriate approach, it=s going to be difficult to collect the data, and, whereas, we may want that kind of data it would be also difficult to say, take a population of patients who have important renal disease, say, coming for AV fistula creation, to say we are going to give you a compound just for toxicity testing, because there=s no chance of showing any efficacy here because they are very unlikely to need any blood to begin with.

DR. SILVERMAN: Toby Silverman, FDA. Please tell me how I can mandate that a patient undergo a surgical procedure that the surgeon doesn=t want the patient to undergo in the first place.

DR. WEISKOPF: Well, exactly, that=s what I=m saying, is that I think you=ve taken precisely --

the only approach you can take, and I=m trying to do is pointing out that you are unlikely to accumulate the sort of data that some members of the panel would like to see. That=s the world we are living in, and that=s -- you can=t do any better.

DR. VLAHAKES: I disagree. The patient population we are seeing has tremendous co-morbidities, at least looking at it from the standpoint of cardiac surgery, particularly, with respect to other -- particularly with respect to renal and pulmonary problems. They are elective because they walk in with a suitcase, or, you know, they are not going to the operating room at midnight, and then there are some subtleties to the definition of elective.

But, if you want to study patients that have important co-morbidities, the cardiac, the vascular, and the elderly orthopedic, they are going to be there.

DR. WEISKOPF: That=s certainly true for the cardiac, you are correct, and I wasn=t thinking about those, but certainly these compounds are being studied in populations other than just cardiac. Vasculars, whereas they have the disease, most vascular surgeons have gotten sufficiently good these days, that transfusion is becoming, if not vanishingly small, far

decreased, and there are few elective vascular cases that require a fair amount of transfusion these days.

DR. JOYNER: You=re right, and that=s part of the problem, people are getting good enough where there are a lot of minimal transfusions with big operations.

The second question, the second issue, though, I agree with Doctor Vlahakes, is even if people, orthopedic patients for example, who may or may not have surgery that will require transfusion, if they are older, and even if they have normal creatinines and so forth, if you go and do the calculations their renal function is really pretty low. And so, there are a lot of these people that look pretty good, but if you actually go and say what fraction of their renal function is normal, what fraction of their pulmonary function is normal, the age related changes and mild co-existing disease put these people, while they are not in overt renal failure or anything like that, I always like to say that these people are just a few nephrons away. So, there=s a lot of really well compensated old people that are doing pretty well and things are going well, so the question becomes, will these compounds either keep them from decompensating or make them decompensate at a greater rate.

DR. NESS: Part of the problem with some of the co-morbidities in elective surgery for some of these studies may be that we=ve coupled them with ANH, where in general, in terms of controlled patients, most people who have major renal failure, major cardiac disease, you wouldn=t want to do a hemodilution in any case, and then doing the hemodilution using the blood substitute as a vehicle would seem to be particularly even, perhaps, more risky.

So that, perhaps, what one would need to do, in terms of considering elective surgery studies, is use patients who are likely to have hemorrhage, who are going to either need blood or need something else, and have them as the vehicle, rather than always trying to do the elective surgery studies coupled with an ANH sort of model.

CHAIRPERSON KLEIN: I=m not sure whether I heard consensus here or not. In fact, I am reasonably sure -- I=m reasonably sure I haven=t heard consensus here.

DR. CARSON: Well, let me, I mean, since it seems to be Dick and I who are disagreeing all the time, but I actually don=t disagree with much of what he said, because you are clearly not going to have lots, and lots, and lots of patients with, you know,

creatinines of five, and, you know, FED 1s of 900 ccs, but you are going to have a mixture of patients, and if you take all comers you will begin to accumulate a database, whether it will be enough to -- it won=t be enough to have, you know, great confidence that you are not dealing with problems, but you=ll begin to accumulate a database. And if events are occurring commonly, you=ll pick it up. If they are occurring in the usual rates then you won=t get -- you won=t be able to detect those kinds of problems until Phase IV.

And, the last point to make is that, who gets blood? Older people get blood, and older people have co-morbidity, so there will be a modest amount of co-morbidity in whatever population you choose to study, but it won=t be -- you are not going to have huge numbers.

So, I don=t think we actually disagree very much on this question.

DR. WEISKOPF: No, I wasn=t suggesting that we did, I think we were agreeing, and it=s only an issue of quantitation that we are talking about, whether or not enough data will be accumulated to be meaningful.

DR. KRUSKALL: There=s an interesting orphan group of patients that I=ve been struggling with how we

are going to get data, in terms of how to treat them, and those are the individuals with warm autoimmune hemolytic anemia, for whom blood is difficult to find, and for whom I know I=ll be sorely tempted to want to use one of these substitutes should they come close to or reach licensing.

And, it=s a particular worrisome subgroup because they are largely older patients, so they have the co-morbidity we are already talking about, plus they are struggling with their own increased free hemoglobin loads based on the hemolysis.

And, I=m concerned that whatever models we use push and study co-morbidity so that we can understand whether we can safely use blood in the situation.

I also am wondering whether it=s possible to put together a study that allows us to accumulate these patients in a small fashion, because I think many people have contacted the FDA for compassionate use for these substitutes already, and there will continue to be some pressure to do that. It might be worth its own separate study as we go forward.

DR. NESS: Well, I would share that issue, obviously, for the warm autoimmunes, but I think an even potentially larger group who could really benefit

from this that we haven=t talked about, and it=s often in perioperative situations, is patients with sickle cell anemia, where the standard of care now is that for many large surgeries many people still do a perioperative exchange with four or five units of blood, about a third of the patients who have been chronically transfused are already allo-immunized, such that it is difficult in many of the cases to find the blood to use, and then if you do the exchange a couple of days before, they often have made a new antibody at the point where they are in surgery, so their bottom is falling out, and then you have nothing to give back because they=ve made a new antibody, everything is incompatible, and you are really in a mess.

And, it would seem to me that one of the very attractive potential uses of one of these oxygen carriers would be that instead of doing the exchange you could do an infusion of one of these materials. You could raise the hemoglobin transiently, which is not a problem because you only want it transiently raised. You could, perhaps, lower the viscosity. You wouldn=t be exposing to new blood with the risk of developing new allo-antibodies in the perioperative setting, or even for other kinds of acute events, chest syndrome or other kinds of things in sickle cell

anemia. These materials, I think, have tremendous potential and I think it would be nice to have the group or the FDA consider applications in these needs as well.

CHAIRPERSON KLEIN: Just a quick follow-up on that, Paul. Are we sure that there aren=t allo-antibodies produced? How carefully has that been looked at? I know it=s extremely difficult to produce an antibody against native human hemoglobin. These compounds aren=t native, and in most instances they are given once, and frequently the search for antibodies to neo-antigens ends a couple of weeks after the administration of the compound.

DR. NESS: Well, I obviously don=t know the answer to that, but I assume that the manufacturers have been asked by the FDA to show evidence of that sort. I think, even with the products that are made from outdated red cells, that the purification is sufficient, so there isn=t enough membrane left that probably would be allo-immunizing, have capacity to allo-immunize, and, obviously, that would be a concern that would need to be addressed.

CHAIRPERSON KLEIN: This actually takes us relatively nicely into the second part of Section III, and we addressed this, or you all addressed this to

some extent yesterday already in the trauma setting, but we are moving on to safety endpoints in the surgical setting, and if you have a single pivotal trial in a stable elective surgery population, what safety endpoints are most likely to predict adverse events at higher risk? And, we=re going to be talking again about how one might power a study with such adverse events.

Would anyone like to start with the surgical patients? We heard something about the trauma patients yesterday.

DR. VLAHAKES: Well, if you are designing a clinical trial in a large number of patients, that the patient population should be broad and should encompass a wide age range, and the purpose of doing this would be to also include patients that may have undiagnosed co-morbid conditions, and I=m thinking specifically of cerebral vascular and cardiac vascular disease. The safety endpoints should look at all organ systems, as have been done in Phase I and Phase II of clinical trials, with the idea being that you will have, in a large number of people, patients at risk.

I think some decisions have to made about known coronary disease, for example, patients that have either mild stable angina managed under medical

therapy, or having elective surgery, there has to be some discussion about whether or not those patients should be included, since a broad application will include patients who may have occult disease, I would suggest that they be included. Some patients who have pre-existing mild chronic renal failure, COPD should be included, and a decision made about whether or not patients with known cerebral vascular disease to some degree should be included, but a broad patient population covering a wide range of ages where toxicities in all organ systems are examined.

CHAIRPERSON KLEIN: Given the known toxicities, or what we think are the known toxicities, are there specific things we ought to be looking for right now in these kinds of studies?

DR. VLAHAKES: Hemodynamics, the GI, the cardiac, and for including the fluorocarbons, the hematologic, infection issues following surgery with respect to host resistance.

DR. CARSON: I think it=s the traditional things that we worry about in a clinical environment, you know, the post-op infarcts, heart failure. I think that infection is an especially important one that is one of the big problems that people develop post-op, and all the hematological stuff, there=s, you know,

drugs, the unexpected things that happen are often related there, and you are worried about the renal function and hepatitis. You know, I think it=s all the traditional issues that we face, you know, in a clinical environment.

DR. VLAHAKES: The issues to be examined in the pivotal trial between Phase I and Phase II, extended Phase II studies for a given material under consideration, the potential issues should come out from the database generated for a given product in those early studies.

CHAIRPERSON KLEIN: Well, we=ve heard increasingly about the increased numbers that are being required to try and be relatively certain that we are, in fact, finding the common toxicities powering up the studies for safety. Do you have any comments about that that might be of help to the agency?

DR. VLAHAKES: If you are looking at -- if we are saying today that in Phase I and Phase II studies we=ve developed a notion of what the material safety profile may be, but we are all concerned that when we expand its use to the older patients and more co-morbidities, if you are thinking of expanding the spectrum of patients you are going to have to have the numbers. If you are looking for things that may not

have shown up in Phase I and Phase II studies, you are going to have to have the numbers.

And also, as a clinician I=d want to see those, I=d want to know that if something proved to -- in very stable studies, and a stable patient population, and normal volunteers in Phase II studies that nothing turned up, I=d like the envelope pushed a little bit because my clinical practice anyway requires that I do that with almost everything that I have used in the past, where things have turned up following approval, most notably, the agent aproteinine that is used a lot in cardiac surgery. When that started to be used in the patient population we are seeing, we began to see renal failure that was really not a major issue either in the European studies or in clinical trials in the U.S.

So the numbers, although it makes the pivotal studies more complex, it makes them more expensive, it makes them take longer, we have to have the data obtained from large numbers of patients.

DR. WEISKOPF: I agree in concept that we want to be finding out as much information about toxicity, about all of these compounds, as we do about all drugs before they are used for the general population. On the other hand, I don=t think it=s

reasonable for us to tell or recommend to the FDA that they have criteria that are more stringent than they use in general for any compound or any drug that they seek to -- that has asked for approval, that we be careful not to single out this class of compounds for some special notoriety that requires an "n" of several fold more than other compounds might be.

If there are special issues that we think ought to be investigated particularly, then I think we should definitely make recommendations about that, but to just, in general, accumulate more data than is ordinarily asked, to me doesn=t seem like a fair thing to do.

DR. VLAHAKES: Well, if you design a clinical trial where you have pages of exclusion criteria, as you might have in Phase II trials to eliminate people that you are worried about where toxicities may show up, yet clinicians may want to apply the materials to these so-called Asuper patients,@ your hands are tied. I mean, you know, if a vendor goes into the regulatory process with exclusion criteria that have been applied to the clinical trial, don=t they have to live with those following approval? And it ties a clinician=s hands medico-legally, for example.

So, the question is, you know, how do you break out of the envelope you create by defining the risk profile of the patients? The only way I can see you break out of that is that you build it into your pivotal trial.

DR. CARSON: The traditional number of patients that I think the FDA is requiring has been 3,000, which maybe -- you know, that would pick up -- that would exclude, at that rate, greater than one per 1,000 in people exposed.

The problem here, and I=m sensitive to the issues that Dick is bringing up, is that we think we have a very safe alternative product, which is allogeneic blood, and so if you were to contrast, the whole rationale, except for a lot of the situations that Jim=s been mentioning, but in elective surgery the whole rationale to use these agents is because they are safer, we hope. And so, it seems like the burden of proof here needs to consider that, and I think that=s a dilemma. I=m sure that=s the reason why this question is on the table.

And so, you know, it=s not the usual situation that we face in approving a new drug. We think we have a very safe alternative treatment here.

DR. WEISKOPF: I understand and appreciate

what you say, and in large measure it=s correct. On the other hand, many drugs are approved that are not necessarily any more efficacious than the drugs that are already marketed.

I=m sure in our daily practice we can think of many examples where a new drug comes on board, which really isn=t much different from its predecessor, and yet, there it is.

DR. CARSON: You mean like the 30 non-steroidal anti-inflammatory drugs, as an example?

DR. WEISKOPF: Well, in our practice like neuromuscular blocking agents are used in the operating room. We have any number that are perfectly safe to use, and yet, every year or two there=s a new one that=s marketed.

DR. COHN: Making the assumption that we want it to be as safe as blood, I=m not sure it necessarily has to be safer, because there are many situations where this will be invaluable and blood is not available, and I=m not just talking about the pre-hospital and combat casualties, I=m also talking about all the hospitals where there is an insufficient blood bank, or there is no blood bank, places where they load up a trauma patient or a sick GI bleeder and ship it into the medical center, they don=t have blood

available. But they could have blood substitute available, and they wouldn=t need a blood bank to type and cross patients, et cetera.

So, I think that in terms of safety, you know, we would like it to be not harmful to the patient, but it=s certainly going to be -- these products are going to be available in ways that, you know, the blood is just not available. So, I think that there are many opportunities. This is not like another anti-hypertensive drug, this is to say, a hypertensive drug where there is nothing right now, you know.

So, I really, I urge us to try to find a way to show reasonable safety in an expeditious way, so we can get this to the point where we can use it.

CHAIRPERSON KLEIN: This is in keeping with the comments that were made at the end of yesterday=s session, if one could demonstrate that any of these compounds were as safe as blood, and carry oxygen, that that would be sufficient in your mind for getting something on the market, and let the market determine then whether and to what extent these are better than blood.

DR. COHN: You know, unfortunately, you=ve got sort of a risk -- you are trying to analyze the risk benefit. Doctor Holcroft has -- this is something

I have to deal with every day, he commented on the person who has a head injury and is hypotensive. That=s an every-day occurrence. We have millions of head injuries, literally 2 million head injuries in the United States, and they are dying at a great rate.

When you contrast, you know, that with the fact that maybe a couple of patients may have a little bit of pancreatitis, okay, that receive this medication, versus saving a considerable number of lives potentially with the use of a blood substitute in the pre-hospital setting, I have to react to the fact that I=m very frustrated by the fact that I have nothing I can do for these folks.

Pancreatitis, I can put the person in PO for a week, right? If they get a little bump in their renal function, I won=t give them a contrast load the next day, all right, but I have nothing that I can do for all of these scores of patients that are dying because there is no way to give them an adequate oxygen delivery out in the pre-hospital setting. We are talking about, you know, an epidemic proportion of patients.

DR. HOLCROFT: Couldn=t agree more. I mean, that=s the point. We are talking, trauma kills patients, and about half the trauma deaths are caused

by head injuries, or the head injury plays a major role in it. So, I guess, but with respect to your -- as I understood your question, Doctor Klein, the one you just posed, you were saying if we could show that it was equivalently safe to allogeneic blood would that be reason to license it, I think that was your question. Is that right?

CHAIRPERSON KLEIN: And carries oxygen.

DR. HOLCROFT: And carries oxygen, right, yes, that=s a good point. Thank you.

DR. CARSON: And, delivers it, too, right?

DR. HOLCROFT: And, delivers it, too, and off loads it, that=s right, it=s got to do a lot of things.

As much as I would like to say yes to that, I would still say no. I would still want to see a study showing that it actually makes a difference, again, in trauma patients, or maybe in the sickle patients. Now, that=s something I hadn=t thought of at all, or a patient with hemolytic anemias and so on.

I=d like to see a benefit in those patients, because it=s possible, you see, that for the head injury patient that maybe you don=t need the hemoglobin, maybe all you really need is just volume and pressure, and so it might be possible to achieve

that with acellular solutions, it might be. So I=d like to see some efficacy for those patients.

DR. KRUSKALL: I think if it=s equivalent in safety to blood, and it carries -- transports and delivers oxygen, that it is licensable for the indications that Paul and I have been talking about. And, I think the magnitude of the market doesn=t concern me as much as the fact that there would be a starting utility for it.

I still am worried about organ damage. I appreciate in the setting of trauma that this would be wonderful to have and the tradeoffs are terrific, but I think about the horrendous problems that could occur if the organ injury is additive in an older patient, and also the potential for the mess that=s created medico-legally if it=s used in a situation where, perhaps, its indications were questionable and these complications occurred.

I think the problem is that we have too many markets that are of interest, in terms of this product. We have no choice but to hedge our bets and simultaneously look at trauma trials and something that=s very elective. In fact, if we look at what are really poles of extremes of use, I think we actually would cover a very big array of potential indications,

but we have to have studies at both ends.

DR. CARSON: Harvey, you brought up equally safe to blood. I mean --

CHAIRPERSON KLEIN: Not identical, but equally safe.

DR. CARSON: -- but, you know, I mean, that=s not achievable in these kinds of studies. I mean, then we could pull Steve Gould=s slide out of 64,000 and those are the kind of numbers you are going to start to look at. I mean, it=s going to be -- you are only going to be able to get that kind of safety parameters in post-marketing, and I think these drugs, if they get marketed, and I hope they do at some point, then the FDA should require a post-marketing study so that we have that information.

Can I bring up another issue, which is not on here, about efficacy, how we are going to prove efficacy in elective surgery?

CHAIRPERSON KLEIN: Yes, but before you do that I think we=ve got a comment that was waiting.

DR. JOYNER: I want to make a comment about the safety issue and the trauma trials, and the trauma surgeons here, true to their training, personality type, MMPI scores and so forth are anxious to have something to do to these desperately ill patients who

they see die at regular intervals, and they would rather do something than not do something, which is why they are good at it.

And, Doctor Holcroft=s comments about head injury are important, and maybe you could help those people, maybe these compounds would be terrific for them and they would have less neurologic injury, in addition to savings lives, and even if you didn=t save any lives if you just had people that were more functional when they got out of the rehab unit that would be a great, great, great achievement, you know, for your people in wheelchairs slobbering.

But, the issue is, in many of these injuries you are going to have disruption of the blood-brain barrier, and with some of these hemoglobin compounds I think that for a variety of reasons you want to be careful before you put hemoglobin next to the brain, that=s the first thing, and the second thing is, even though these compounds might have been seen as safe in one environment, they may not be safe in another environment. I really agree with Doctor Holcroft, you are going to have to do a trial because I think you license something, you say it=s safe, or it=s good enough, and, you know, you need to be brutally intellectually honest with yourself before you don=t

make somebody do a trial, a well-designed trial. I think you are really playing with fire there.

DR. WEISKOPF: I=d like to bring up an issue which we have been talking about but sort of skirting around. I really would like to confront it head on, because it has been bothering me for the past day and a half, and that has to do with off-label use.

I=ve heard a lot of the panel discuss issues related to safety, which are generated by the concern for off-label use, and it is my understanding, and I would like, I guess, comment from somebody, some relatively senior person in the FDA about this, because it will straighten out, perhaps, my understanding -- it=s been my understanding that a product is licensed for whatever the studies can support, and that then it is up to an individual physician to decide whether or not they want to take whatever risks are associated with off-label use, and that the FDA does not take any official position about that. And so, the issue here is, are we -- is it appropriate for us to be concerned about off-label use? And, many of us, for many years, have used many drugs in off-label use. We all take that individual risk and go on with it.

CHAIRPERSON KLEIN: Does anyone else on the panel want to comment on that?

DR. CARSON: Happens all the time, and it=s going to happen here. I mean, there=s not a chance it=s not going to happen.

DR. WEISKOPF: Well, yes, it=s going to happen. The question is, do we force somebody to do studies for which they have no desire for that in their label? Is that an appropriate thing?

DR. SILVERMAN: Let me just give you my basic philosophy here. You are right, people get a label for what they study. It does not absolve us from responsibility when we know that a product will be used, and in this case probably massively, off- label. I think we have a responsibility to ask manufacturers to study a product when they know that it will be used in that way.

I also think that, you know, each of them probably has an intent at some point to market for most of these indications.

DR. AEBERSOLD: If the agency has a clear indication that a drug is sold vastly in excess of the labeled indication, the agency actually has legal authority to force the company to study the off-label use, so that it can be demonstrated or assessed whether it=s safe and efficacious in that, and that=s for a marketed drug. What we are asking, you know, let=s

consider this question up front, rather than, you know, find out ten years after a drug is on the market that it may have been unsafe. We do have the legal authority to force a company to do studies in an off-label indication.

DR. WEISKOPF: After it is marketed, if it=s used after it=s marketed in an off-label indication.

DR. AEBERSOLD: Right. Let us recognize that, you know, there are beachhead indications where you get on the beach and you want, you know, to market it to the whole continent.

DR. HOLCROFT: How many times has the agency done that?

DR. AEBERSOLD: I don=t know the answer to that.

DR. SILVERMAN: I don=t know the answer either.

DR. WEISKOPF: You=re talking about after it is marketed and there is substantial off-label use, as opposed to prior to marketing, am I understanding you correctly?

DR. AEBERSOLD: I know that that can be done for a marketed drug.

DR. WEISKOPF: Sure, right.

It was different from what Doctor Silverman

was talking about, about a responsibility beforehand when one has certain beliefs in indications.

DR. AEBERSOLD: If it=s widely known that the marketed indication would be vastly in excess of the sought indication, I think we can address the issue in the pre-licensing stage as well. I mean, we=ve all heard, I think Doctor Joyner said very clearly yesterday that, you know, if it was shown safe for two units in surgery, he=d love to use ten units in the trauma setting, if I=m remembering that comment accurately, and I think that that indicates a potential for use in areas that haven=t been studied.

DR. JOYNER: I don=t want that quote ascribed to me, somebody else said it.

DR. AEBERSOLD: Sorry.

DR. COHN: Just to comment, in the 95 minutes of this meeting, 332 people have died in the United States from trauma, okay? This is not a minor problem. As many people as in this room have died from traumatic injury, and I think that this is not your typical situation where we are talking about another anti-hypertensive medication, we are talking about the potential of using something that has got a considerable amount of benefit.

I=m not ignoring, you know, the fact that

we want this to be safe, and I agree that you cannot show, you know, in a trial of two 100,000-person arms I think that there is a certain urgency here, and I think that we need to consider that when we are talking about this drug. Maybe these drugs are things that need to be looked at in a planned post-licensure marketing analysis, so that we can get, recognizing that there is going to be -- frankly, let=s look at it a different way -- the cardiac surgeons are not going to start using this in cardiac surgery tomorrow because they have a perfect -- if it was licensed today it=s not going to be used because we have good alternatives.

Fibrin glue was approved last year, we don=t use hardly any fibrin glue at our institution, despite the fact that we are doing a whole lot of surgery that could benefit from fibrin glue, because it=s very expensive and there are certain logistic problems with using it. Okay. Just you because you license it doesn=t mean everybody is going to abuse it, but there are situations where it will be extremely valuable and that the risk benefit ratio is going to be far outweighed by the benefits.

And, yes, maybe it will be shown to cause some unexpected small incidence of adverse effects, but we=re talking about using it in situations where the

mortality is already 90 percent. If a few people get unexpected pancreatitis or something like that, I mean, this is a unique situation.

And, while I=m speaking, more people are dying. So, I=m not trying to be theatrical here, this is a fact, and we don=t have any answers to it right now.

DR. VLAHAKES: Speaking about rapidity of deployment and use in clinical practice, the vendors should be aware, and I=m sure you are, if this was approved tomorrow, and given the fact that blood is the alternative, the budgetary process in most large hospitals is immense. And, again, this is separate -- probably separate from the regulatory issues, but a concern that all of a sudden it=s going to go into 100,000 people the day after approval is very unlikely, given the kinds of fiscal restraint that we will face if we want to use it in clinical practice.

We=ll have to justify it on a risk/benefit cost basis, probably to the Blood Bank Committee.

DR. CARSON: But, I=ll predict that patients= demands for these drugs will move these drugs rapidly into the marketplace, because, I mean, you only have to watch the trend in blood safety that is present now with all these new tests that are picking up three

cases of HIV in 13 million units of blood transfused, that there=s such a demand to get zero-risk blood that alternatives are going to be warmly received, even though, even though it may be completely irrational because, you know, the prospects that these drugs are going to be as safe as blood is -- I mean, that=s, I mean, statistically I think it=s unlikely, just by --

DR. COHN: But, if a patient -- I=m sorry -- but, if a patient came in and said I want to use the new blood substitute, and you said to him, if I used it 24 hours later it will be gone and, therefore, I would have to give you a unit of blood anyway, you have to clearly explain it to them. This is not the lap. coli. issue, or the patient saying I want a smaller scar. They are going to rely on us, okay, to do the best thing for them.

And, if we are going to end up giving them the cost and the risk of a blood substitute followed by the unit of blood anyway, then, you know, I just think that it=s not going to be lay people charging in line to get a bridging blood substitute when they are in hemorrhagic shock. I just doubt that that=s where we are going to be using it, and for some of the financial reasons you have mentioned.

DR. JOYNER: The financial reasons are quite

interesting. Again, I want to distinguish between elective use and I think what Doctor Carson is talking about in these shock issues. All of us here work at academic centers where there=s reasonable peer review. There=s a Pharmacy and Therapeutics Committee, to get certain antibiotics it takes an act of God, plus an ID consult, all sorts of other things.

But, if you look at data that=s been in the New England Journal and JAMA, only 30 percent of the people that could benefit from beta blockers that have cardiac events in community hospitals are getting beta blockers. If you look at aspirin use in post-MI patients in community hospitals, it=s way down, as opposed to academic centers where people are doing pretty well.

So, I think for us to think that the average physician out there is going to, (A) keep up with the literature; (B) deal with the use of these products in a subtle and intelligent way, or if they have any interest in it, is nuts, and there=s no evidence to support it.

I mean, the practice out there is pretty bad in a lot of areas. That=s point one.

Point two is that you are a private practice orthopedic group, and you start promising

every grandma that comes in that you are not going to give them blood, you know, how long will it be until that=s an advertisement in the Miami Herald? Pretty darn fast. And so, I think that if the public=s perception of risk of blood is way of whack in comparison to things not like non-steroidal anti-inflammatory drugs that do, in fact, kill a lot of people every year, I think that the public is second only to the many private practice clinicians who don=t understand some very straightforward and simple things.

I think we=ve got to be careful. I think it would be used completely -- like, using aproteinine, I mean, again, in our institution fibrin glue, you are right, all these things have been used intelligently, but I=m not sure they=d be used intelligently in the outside world.

CHAIRPERSON KLEIN: We=re a little off the point, but I think we have time.

DR. JOYNER: No, I don=t think we are off the point, because I think off-label use is going to be a problem. I think expecting people to -- the assumption here, because we work in academic centers, that people are going to use these rationally is subject to challenge.

CHAIRPERSON KLEIN: We have time, and I

think this is an important issue, and I want to ask the panel members, many of whom have practices dissimilar from my own, and that is, assuming that something is marketed, say, for a surgical indication, and yet, people want to use it for a number of off-label uses, I=m assuming, (A) that the average practicing general physician is not going to have access to these kinds of drugs for either financial reasons or because there=s a practice guideline that=s set up by the equivalent of a PT committee at an academic center. Is that essentially what you are saying? It=s not going to there like aspirin to give, even if the average physician had read the literature and said, yes, this is something that we need to use.

DR. VLAHAKES: I think, just to look ahead a little bit, using this in sufficient quantity or with repeated dosing to ultimately avoid one or two units of blood exposure for, let=s say, a cardiac surgery patient, that=s going to wind up adding, let=s say, a four figure amount of money to the patient=s bill. It will go to committee, there will be a risk/benefit analysis against blood, and there will be a practice guideline. Practice guidelines used to be suggestions in the past, they are now coming down on us in a slightly more forceful manner.

And, just for the vendors who are going to be marketing later on, the television commercials aimed at the patient population work for some things, but they are not going to work against panels of experts within hospitals. So, keep that in mind when you price and ultimately go to sell.

DR. JOYNER: I think that there won=t be panels of experts at hospitals. I think if you look at my home town in Tucson, the cardiac surgery data in private practice hospitals in Tucson indicates that nobody has ever read those, nobody is even aware of that New York State experience, because they violate every key element of it. So, I think that our faith that people out in the community are going to be subject to even 50 percent of the types of restraints or peer review we are is just not supported (A), and (B) that in many of these community hospitals in highly-competitive areas where there=s a couple cardiac surgery programs, if some cardiac surgeon wanted to do this, and was told no at one place, he would threaten to move his program, his bed days and his ICU use elsewhere, and they=d be welcoming him with open arms.

So, I think that these people are not subject to the type of peer review we are, and I don=t think there=s any -- and the financial stuff may be

helping, but I don=t know if it will do as good a job as the types of P&T committees and mandatory consults they use B and stuff like that do for us.

DR. WEISKOPF: I agree with the thought that to a large extent the use of these compounds will be fiscally controlled. I would guess, and I guess I have no firm reason to believe, but I would guess that these compounds will be relatively expensive to use, and any individual unit, however it is marketed as a unit, will be relatively expensive, and that these days any hospital administrator, in some form, whether it be through committee, or whether it be through a pharmacy, or whether it be through a blood bank, wherever these get eventually dispensed in a given institution, will look at that cost very carefully.

Even for relatively low-cost drugs, we are now -- many institutions are now under great pressure to reduce costs of even what we used to consider as relatively low-cost drugs.

DR. KRUSKALL: Well, we don=t actually know what the cost of this is going to be, and it embarrasses me a little bit to think that we would abrogate our responsibility to the hopes that the finances would work out in our favor. If they don=t, or if there is some creative solution that short term

allows these to be disseminated, then, in fact, we haven=t plugged a hole that we=re trying to deal with. So, I wouldn=t count on that.

DR. WEISKOPF: Well, it embarrasses me as well, but that=s what=s happened to the medical system, and what=s happening, you know, to much of our medical system is an embarrassment.

CHAIRPERSON KLEIN: I think we=ll move back a little bit and try to address at least one of the aspects of the question that was posed to us by the agency, and that is, in the situation where you have a single pivotal trial in an elective surgery situation, and we have a number of those ongoing right now, what is the increase in adverse event rate that should be ruled out before commercial availability? That=s your last question here. And, should this increase vary depending upon the rate of adverse events in the controlled population? If so, how? Not an easy question, but let me open that up.

DR. HOLCROFT: I=m willing to start.

If, say, a sickle cell patient, or a patient with a hemolytic anemia, then I=d accept some adverse events. If it=s just a routine, I don=t know, let=s say, Aroutine hip,≅ or an aneurism resection or something, where we have a very good product which is

very safe, then I=d demand that the adverse event rate be very low.

DR. KRUSKALL: See, that=s because you are a trauma surgeon. I would feel exactly the opposite. I=d be very concerned about adverse events in warm autoimmune hemolysis, it is a very tricky situation, and there certainly have been patients who have died for lack of blood. But, we sweat as we do find ways around the situation, and although I would like to improve the speed with which we find blood, I=m not sure that I could tolerate an adverse event rate the way I could imagine tolerating it in trauma where the mortality is so high.

DR. HOLCROFT: Well, I don=t know anything about hemolytic anemia, so that=s fine. I=ll be happy to accept your analysis.

But, I guess what I=m saying, if there are cases in elective surgery, and that=s what I kind of thought you were saying earlier, where the problems of giving allogeneic blood were enormous, then under those circumstances, and I don=t know what those circumstances would be, and you guys would know, then I=d be more willing to accept a side effect. That=s all.

Now, maybe there aren=t any cases. Maybe

you -- it seems in our hospital that, at least in my patients, in surgical patients, our blood bank somehow always manages to come through, and I don=t know how they do it, but they just -- they do it. Now, sometimes it takes them 24 hours for an elective case.

And, if that=s the situation, then I=d have to concede your point. But, are there cases where blood banks can=t come through in elective surgery?

DR. KRUSKALL: I think that there are relatively few, and it is the work, and the risk, and the resource allocation that goes into solving these problems that makes this, to me, so appealing, and also makes a high rate of adverse events less tolerable.

But, we don=t know that we are there, I mean we may find a product that is equivalent in terms of adverse events that would be very -- has very few adverse events and would be very acceptable. I don=t know how to put a limit on it, but my threshold would be low.

DR. NESS: Yes, I think that at a place like Hopkins, we=d probably have a handful of cases a year where we get to a situation either for elective surgery or somebody even in the ICU, I would really want to use a blood substitute if it were available because there really is no other alternative that I think is not

within an acceptable degree of risk.

Having said that, I think the real problem is that I think I can make that decision pretty clearly, because I think I know the risks of going ahead with blood in those situations, and I think I would know the benefits of the blood substitute, but not everybody is going to be in the same situation to make that judgment and, obviously, the concern would be that some people would quickly leap to doing something rather than wait the 24 hours to find compatible blood, which might be the ultimate solution if they were willing to wait.

DR. HOLCROFT: I stand corrected.

DR. JOYNER: I would have to talk to the blood bankers in Rochester, but it=s my impression, because I talk to them all the time, that they have similar numbers that you have. Through hard work and, you know, we even have a number of stored frozen units that can be thawed for these really difficult cross matches, and it=s difficult but it never failed us.

And, what=s amazing to me is not the -- it=s the number of people that can do it in less than 24 hours, and the number of people that you have to wait a while for it is vanishingly small, the number of people that they can get stuff for you in three, or

four, or six hours is incredible.

DR. NESS: But, there is a real need. I mean, these materials would be very -- you know, we had a couple cases in the last foreseeable memory that would not have died had these things been available.

CHAIRPERSON KLEIN: Again, this is, in many ways, a temporizing effort, where it may take you 24 hours to get the blood from the frozen storage in Rochester to the coast of North Carolina, and with the 24-hour half life you may, in fact, be able to deliver oxygen, even if the toxicity of the compound is slightly higher than it might be for blood.

Does anyone want to attempt to put numbers on this for the agency? Don=t feel that you must do so.

DR. WEISKOPF: You know, I think they are asking us because they=ve had difficulty answering this question, and I don=t know that it=s any easier for us to answer the question than it was for the agency itself.

You=ve heard a variety of opinions, and there are an enormous number of circumstances that one might alter the risk benefit ratio. There are a variety of different times where the risks vary, and say the clinical risk varies, then there has to -- how

can you put that variable risk into a finite one number for risk for the projected use of a compound or drug.

DR. COHN: On the other hand, I think possibly we could think of this, not as -- I mean, I think it would be -- it would have to be incredibly safe to be replacing blood in the simple elective situation, but if we say that we are going to use it when the, you know, redo whatever case goes bad, or the person who is GI bleeding, or the person who is traumatized, in that situation possibly the level of adverse effects could be a little bit higher. That=s all I was going to say. So, I mean, if you were going to say it has to be one in 60,000, if it was going to be the replacement for conventional blood transfusion, where I think it will be very infrequently, I hope it will be very infrequently used, that would require a different level of safety than if you think it=s going to be used in a liver transplant with 100 units where just having something available will be advantageous.

DR. CARSON: I would ditto the concept that=s being expressed, is that we would be much more tolerant of adverse effects in the trauma situations that Jim is describing for us, and have little tolerance for significant effects in an elective surgery situation where we have, you know, allogeneic

blood available to us.

So, I think the standards would be very different in two settings.

CHAIRPERSON KLEIN: If there are no other comments on this, I cut Doctor Carson off a little while ago, he was going to make a comment on efficacy, or, Doctor Silverman, do you want to comment first?

DR. SILVERMAN: Yes, Toby Silverman, FDA.

The question is very specifically framed, if you are going to have only one pivotal trial, what would you want to see?

CHAIRPERSON KLEIN: Does that make it easier?

DR. CARSON: But, I think it=s the same answer. I think it=s the same answer. If it=s with pivotal trials in trauma then, you know, what we are worried about is different than if an elective.

But, really, what the number you want is elective, you know, and that=s the one, of course, that=s really hard. I mean, if you were to follow through Dick=s earlier comment that, why should we have a standard that=s different than we have for new other drugs, then I guess the one in a 1,000 standard is commonly used. But, I don=t know, it=s very subjective and I=m not sure, I don=t know what the right answer is.

I certainly don=t feel strongly about any of these other, and I=d sort of want it in the magnitude, you know, in that rate, in the magnitude of one in a 1,000 kind of rate, which, you know, I mean, we are talking about exposures of 3,000 patients to be able to get those kinds of numbers.

CHAIRPERSON KLEIN: Jeff, did you want to comment on efficacy?

DR. CARSON: Yes, I mean, I would like to bring up an issue that=s not on your list, but it=s come to mind as I=ve begun to think a lot about these drugs. My understanding is that one of the tests of efficacy is reduction of allogeneic blood use, that if you can demonstrate that there=s less allogeneic blood use in patients randomized to receive these drugs, that that would be considered efficacy.

And, my problem with that is on several levels, and what I=m going to do is just create a scenario for you. I think that the studies as they are currently designed are biased towards finding effect, for the following reasons. One is that most of these studies are set up where basically you randomize patients to be given an allogeneic unit of blood or a blood substitute, that then these people are followed forward in time and then you are counting units of

allogeneic blood on follow up.

I think that design guarantees that you are going to find a difference, even if the blood substitute is doing nothing, and the reason is that, there=s at least two reasons. First is that in the very early parts of the perioperative recovery period those are when people look sickest, that=s when they are physiologically challenged the most, and I think it=s when most blood is given.

And so, you=ve guaranteed that there will be a delay in administration of allogeneic blood to the group randomized to the blood substitute by study protocol, and so when you are then considering whether you should give additional allogeneic blood those patients are less sick than they were in the very immediately post-op period, so that clinicians are going to be less -- are going to be more comfortable withholding blood under those circumstances.

Two is that we are assuming that people need blood in these situations, and I think many of us would agree that we don=t know when they need blood, that many of these trials involve, you know, giving blood at nine and ten grams, and that we don=t even know if they need blood at that level, and certainly if they do the kinds of sample sizes that we are looking

at aren=t going to have a prayer of identifying it.

So that, if you are going to use efficacy as a reduction in allogeneic blood use as one of your standards, then I would argue you have to have a placebo group as a third arm in that trial, because, you know, what you want to show is, you want to prove that, in fact, that that patient didn=t require the blood, and by giving placebo if it turns out that -- actually, I need to think through this some more, but if you don=t have a placebo group then it may appear than you are giving less allogeneic blood, and all you are really doing is creating a situation where they didn=t need blood to begin with.

Am I being clear with this description? And, I think every single trial I=ve seen doesn=t have a placebo group and, therefore, it=s biased to showing an effect, it=s guaranteed to show an effect in efficacy, and I think it=s, therefore, a biased observation.

DR. WEISKOPF: I understand what you are saying, Jeff, and what you are doing, and what you say to a certain extent is reasonable. What you are asking for, though, I think is -- what you are saying is that the vast majority of blood in the United States is given without a firm indication that, in fact, it is needed. But, that is the way we practice, to do the

sort of study that you ask would ask for a paradigm shift in how blood -- how people think about giving blood, and what the indications for giving blood, that would need to change.

And so, whereas the study designs do have certain faults, they reflect the real world practice. What you are asking for is a study that would also combine a study that would say, any sort of option carrier needed at the specific points of study. That=s a different study. It=s an important question, but it=s a completely different study.

DR. COHN: The unfortunate thing is, and I completely agree with what you said, is that if you -- most of these trials are done at the moment that someone decides to give a unit of blood, they either give a unit of blood or give a unit of the blood substitute.

What you=d be asking is that some -- that an anesthesiologist looking at ST segment changes at three millimeters in a patient who just had major bleeding from a cystectomy that got away from the surgeon, and just got a -- you know, this patient is hypotensive, that he has a unit of something in his hand which turns out to be lactated Ringer=s, that he accept that while current practice would be in this

patient who is possibly going to have an MI, that we would give him something that carries oxygen, we are now going to give him something that doesn=t carry oxygen. So, I think there=s a problem with that, because the transfusion trigger has been more or less the anesthesiologist=s lack of comfort with the way things or going, in terms of ongoing blood loss, let=s say.

DR. CARSON: Well first, I=m not suggesting that patient be enrolled in this trial, that obviously if someone is having active ischemia I don=t know that that=s the setting that we=d want to do this kind of analysis in, one.

Two is that most blood is not given intraoperatively, but rather is given post-operatively, at least in studies that I=ve been involved with the vast majority of it is given post-operatively.

And third is that most blood is given for much less clear reasons. So, you know, it=s not usually three millimeters ST segment compression, it=s usually given for much more subjective reasons.

DR. HOLCROFT: I agree with Jeff=s point that, as I understand it, that if you -- but, maybe saying it another way, doesn=t it have to do with using a surrogate endpoint, or saying it this way, if we set

up the studies for the elective surgery, which is the topic this morning, if we are going to say diminished use of allogeneic blood is reason to license the product, in a sense that=s what we are saying, then I would say no. I wouldn=t accept that as a reason to license a product, because of the reason that Doctor Carson just pointed out, because the way these studies are going to be set up, sure, you are not going to use as much allogeneic blood if you have a substitute that would tide a patient over to a questionable time during their care.

So, I think maybe in a sense the question is, what should -- is there a surrogate endpoint?

DR. COHN: Address the comment about placebo. Do you think that you can get -- that you would be willing to give your patients no blood or blood substitute in one arm?

DR. HOLCROFT: Well, let=s say it this way, I=ll avoid answering that question by saying I wouldn=t accept a surrogate endpoint, that=s all. I wouldn=t accept a squishy surrogate endpoint, and I think this is a squishy surrogate endpoint. It=s somehow saying, giving an allogeneic unit of blood is intrinsically bad, as opposed to giving a unit of a hemoglobin-based substitute that is inherently good, and we don=t know

that it=s inherently good, and we won=t know it=s inherently good until we have decades of use with the subjects and to sort of experience with it that we now have with the allogeneic blood, and we have that experience with allogeneic blood, and we know it=s safe, as Doctor Klein pointed out yesterday.

So, I=d be unwilling to substitute something that I know is safe for something that might be dangerous, just for the sake of eliminating the use of allogeneic blood.

DR. COHN: So, I guess -- but I think Jeff=s point is correct, I think that in order to prove this, that the substitute is somehow better than the allogeneic blood, you=d have to have a placebo arm, and I don=t think I would be willing to put a patient in a placebo arm, to answer your question at last as I think this through, but then neither would I be willing to accept the -- neither would I be willing to accept that particular surrogate endpoint.

DR. KRUSKALL: But, the biggest embarrassment of this situation is that we have really no good endpoint. I mean, transfusion is an endpoint, it=s a terrible endpoint, we have no better way of measuring what we are doing. We can=t distinguish between treatment and prophylaxis. We are fuzzy on the

edges, and so I think that we will cripple ourselves if we, at the same time as we are using allogeneic blood transfusion as the gold standard, try to throw it out.

So, I think we have to start somewhere, and as bad as it sounds, in fact, that is a real endpoint. If we use allogeneic blood repeatedly and regularly in the immediate post-operative period to stabilize a patient, that becomes the standard that we are trying to compare against, and it=s a whole separate question as to whether that=s proper for us to do it.

DR. WEISKOPF: I agree with Margot. Unfortunately, we have nothing but squishy surrogate endpoints for transfusion of any red cell component or product, and to then -- so, we have no other way of assessing any artificial oxygen carrier that is proposed to replace red cells for whatever indication. We have to use the same surrogate endpoints. We have no other choice.

To do the hard study that Jeff is suggesting, while maybe scientifically appropriate, is an impracticality under current circumstances.

DR. KRUSKALL: But now having said that, one of the dangers, I think, in these trials is that when the indications for transfusion or use of the oxygen carrier aren=t very rigorously established, then there=s

tremendous room for bias in use of the products, and I think that to whatever extent we can completely codify and rigidify how an allogeneic transfusion is used will make these studies stronger.

Otherwise, there will be a natural tendency to lean in favor of that that we want to work, and it is so easy to manipulate when one should use blood and when one thinks it=s actually effective, since there=s no measure.

DR. WEISKOPF: No, I agree that some studies that we=ve seen in various formats are greatly subject to bias, because if they are not blinded then the only other way that one can -- sometimes it=s very impractical -- difficult in these studies to create a blind, and if we can=t do that the only other control that one could possibly have to eliminate that bias is to have as rigorous as possible indications for transfusion with as little room for maneuvering.

DR. KRUSKALL: I think blinding here, although it=s done, is of necessity almost impossible, just thinking about it from the laboratory point of view. I know about every hemoglobin-based substitution trial that=s going on because of the appearance of the specimens when they arrive in the laboratory. Actually, the same was true for fluorocarbons when we

used those. So, it may, perhaps, have an element of blinding at the bedside, but not for very long, and the information gets exchanged between the laboratory and the clinical services, so I think that even while we blind to the extent we can, rigor is really absolutely critical.

DR. NESS: Yes. Perhaps, part of the problem is compounded by the fact that at least some of the studies we heard about yesterday seem to be searching for very small increments in blood use reduction, for instance, is one unit not used enough of a reduction to really be clinically meaningful, and are we ever going to believe that that one unit that wasn=t used really had to be used? So that, perhaps, in terms of trial design, if this is going to be an endpoint in terms of the reduction of the use of allogeneic blood, that it be designed to get at cases where the reduction would be large, such that the typical patient would use nothing compared to three or four units of allogeneic blood if they had the blood substitute. That, to me, would be a more convincing argument of efficacy than some of these other trials that we are hearing about, where the mean reduction of allogeneic blood use is maybe one unit per case.

DR. JOYNER: The issue about a placebo

group, I=d like to echo comments previously made, is that nobody knows why people get blood, and there=s a complex series of cultural things. Sometimes the physicians are treating themselves because they are nervous, anxious, and so forth. And, you know, this conference is sponsored by both the FDA and the NIH, I don=t know if we want the FDA to force the manufacturers of these products to conduct complex, kind of anthropologic studies about why blood is given, do cultural -- you know, where is Margaret Mead when you need her -- to do cultural anthropology in the hospital, but I think that as the NIH thinks about things, they need to maybe make an effort to try to understand why blood is given, under what circumstances, you know, how can we get people to give less, and whether other things like ANH actually work. S, I think that there=s a whole separate set of issues here that the folks at the NIH should think about, and that is trying to learn more about how and why blood is given, how we might change people=s behavior, and, you know, have like a behavior modification program at the hospital.

And, I think that=s one place you could get maybe more mileage out of your 12 million units a year, but I don=t think that=s the FDA=s job, to tack that on

to blood substitute studies, I think that=s something the NIH should think about, and I don=t know how you do it, but there=s got to be ways to think about it.

DR. COHN: Just to underscore something that Paul said, you know, when you do this transfusion avoidance arm in these studies, in other words, you give three units of blood substitute followed by allogeneic blood, and basically postpone the use of allogeneic blood until the point at which the patient is less sick, the so-called Abridging@ idea, you know, what we may be doing, if we did a placebo arm, would be to demonstrate that they never needed it in the first place, and that just as many people never got allogeneic blood, just the way -- I think it=s the equivalent of what we=ve recently discovered, I think, in the critically ill area, which is, our transfusion threshold, because the patients were critically ill, of ten is now dropped down to seven, you know, at least in some institutions because of data that supports that giving allogeneic blood in the critically ill population where patients require two to four units per week on average is unnecessary, and that in having a more restrictive transfusion policy a third of patients in the critically area, at least in this large perspective randomized trial, never got any units of

blood at all.

So, I think avoidance of transfusion, while it was an admirable goal in the efficacy studies that were being done with the blood substitutes, the lack of a control arm may just be looking at a cultural problem, I mean, basically amplifying a cultural problem, which is, we want to give something, so right now we give allogeneic blood, which is unnecessary, or we give a blood substitute, which are unnecessary, when we could have just given lactated Ringer=s, I guess is what you are saying to underscore that. I don=t have an answer, but I do think that avoidance of blood transfusion, my understanding was, the accepted Phase III outcome endpoint that the FDA had suggested in the past. Is that not true?

DR. SILVERMAN: Toby Silverman, FDA. If you go back to the talk that I gave yesterday, what we said was that it was a surrogate for avoidance in a clinical trial of unmeasurable risks of blood, and that we understood that you couldn=t -- an enormous trial would be necessary if you wanted to actually measure that avoidance. So, it is a surrogate.

I also said that we would be asking companies to tally up how many units of oxygen-carrying, and hopefully delivering, solution, be it the

substitute or blood, they would have to give in order to avoid an allogeneic transfusion altogether in the patients. In other words, you=ll be tallying it up in both arms, in a control arm where the patients are getting blood, and in the test arm, and we will know the answer to how much needs to be given in one group versus the other.

But, it is a surrogate, and we understand that it is a surrogate, for avoidance of the risks of blood. That is why we have put such an emphasis, particularly in the perioperative setting, on the safety side, because we also understand that many of the adverse events that occur post-operatively might be replicated or added to by administration of these products.

So, the safety arm, as I said, is also the efficacy arm.

DR. FRATANTONI: Let me just make a historical point. Lots of people here were involved in the workshop that was held in 1994 on efficacy. A couple of people chaired some of the sessions.

The background to that meeting was that there have been studies going on, some clinical studies and some safety data was being gathered, and in 1992 the American College of Physicians came out with a

statement that was representative of the attitude of the times, which stated that, "Allogeneic transfusion is an outcome to be avoided," which is a shockingly different type of statement than was coming from that organization in previous years.

With that as background, and with no other good ideas coming out of that conference, and the people who presented data were surgeons, trauma surgeons, medical people, and people talking about using oxygen carriers for local regional perfusion, the idea of avoidance of allogeneic transfusion as an endpoint was essentially the last thing left on the table, and it was left as the only thing that the FDA said it would accept at that point. FDA also said they'd accept any other good ideas that may come along. No other good ideas came along.

CHAIRPERSON KLEIN: Thank you.

I think we've pretty much covered the waterfront on safety issues and elective surgery or surgical trials. Are there any other comments that any of the panel members want to make, or are there any other issues that you think we haven't covered that the agency would like the opinion of this panel on?

DR. VLAHAKES: Are you looking for a consensus?

CHAIRPERSON KLEIN: Well, this really isn=t a consensus conference, and I doubt that unless we all went out this evening and had -- yes, enough to drink -- that we=d come up with a general consensus on many of those. But, if you have a consensus proposal, I=m delighted to hear it.

Hearing none, are there any other comments or issues that the agency wishes this panel to address on the surgical trials? If not, I=d like to thank all the participants this morning. We=ve finished with about ten minutes to spare, and so we=ll take a break at this point and come back at 11:00.

Thank you all.

(Whereupon, at 10:20 a.m., a recess until 11:03 a.m.)

CHAIRPERSON FITZPATRICK: I=ll try and read these to you, I know it=s a little awkward and I apologize for that.

I=m Colonel Mike Fitzpatrick, and, yes, I am in the Army, and I am a Colonel. I work for the Assistant Secretary of Defense for Health Affairs, and as moderator we didn=t want to construe this as a DoD forum, so I=m here in civilian clothes. Since I=m moderator, I won=t be supplying opinions, and if I do you can slap me, and they do not reflect the Department

of Defense.

In the last session, what I have been asked to do is help the panel summarize what=s gone on for the past day and a half, and, perhaps, get some points of clarification from them, and if there is someone in the audience who has a compelling need to speak to some of these points we might be able to entertain that, depending on time constraints. If not, Paul Aebersold and Toby Silverman will gladly accept any written comments from anyone at their offices, by E-mail, by phone, and if you have comments pertinent to the questions, or relating to questions asked of the panel, please feel free to contact them and submit your comments to them.

The first question the panel was asked, and I=ve been trying to summarize, certainly not made all the points that were made, I=ve tried to kind of get the Gestalt on what the panel has, we will have a transcript, we will go through that in detail. We want to make sure that we have the essence of what you felt before you leave.

The first question was, should mortality be the endpoint of choice in hemorrhagic shock or exsanguinating hemorrhaging. We had a number of people say yes, but there was a lot of discussion on that,

that it could be ambiguous, that surrogate outcomes may not be necessary, but on the other hand there are surrogate markers that should be evaluated, that there=s a subset of clinically significant parameters, that I=m not sure we defined exactly what that subset is, that needs to be looked at, and that this may not be the all-encompassing group of parameters that have been previously looked at. And, please jump in here if you have comments or have specifics you=d like to add.

DR. HOLCROFT: I=ll talk a lot in the next 25 minutes, because I have to catch a plane, and then you won=t have to listen to me anymore.

But I agree with what you say, although I don=t -- I think mortality is about as unambiguous as you can get, so I don't think that=s a problem.

In terms of clinically significant in vitro parameters, you just said we are not sure what those are. I=m sure what they are. It=s neurologic outcome, and that=s clearly definable, and that is significant.

I suppose if you showed that you had an agent that had kind of plus/minus effects on survival, but the patients who received the experimental agent, all of them went into liver failure, then I=d say, sure, that won=t do, but unless it=s something like that I would be satisfied with survival and neurologic

outcome. And I wouldn=t accept anything less than that.

Thus, use of allogeneic blood, I wouldn=t accept that, not in this setting, not in this setting in trauma. Cost, I probably wouldn=t even accept that. So, I would want one of those -- I would want one of those two, mortality, neurologic outcome, that would be my vote.

CHAIRPERSON FITZPATRICK: Right. Thanks.

Anyone else have comments about the clinically significant issues?

DR. HOLCROFT: And, I=ll make one last point on this. You won=t need 64,000 patients in each arm, because if you select the patients properly, again, the patients with the head injuries, if you put those patients in, then you are going to have a very high mortality rate, which means that you have the potential for improving it, and so it=s going to be on the order of hundreds of patients, perhaps, in an arm. It won=t be anything more than that. So, maybe 500 in an arm, something like that, would do the trick.

DR. WEISKOPF: As you know from my comments yesterday, I=m not particularly happy with the thought of only using mortality as an endpoint. I think something more sensitive, again, ought to be used. I

can go along with Jim=s idea of neurologic outcome in a graded way, and I would take the other approach, I would exclude patients who have a neurologic injury upon entering the study. That=s a separate issue. Looking for neurologic toxicity, I believe, is important based on some of the preclinical and clinical data that we=ve heard about, but that is, I think, a separate issue, maybe there needs to be a separate study in just neurologically injured patients, whether that makes an impact, and to determine any neurologic impact upon patients who have not had a neurologic injury I think is an important issue.

In terms of something that is -- that death, while as you say is unambiguous, you just go around and count the toes, does not tell you about lesser important injuries which can be very important.

DR. HOLCROFT: If you exclude the patients with the head injuries, or saying it more specifically for purposes of a study, if you exclude patients with low Glasgow coma scale scores, and I=ll define that as eight or less, then the survival is going to be so high that you are not going to prove any benefit from introduction of an experimental arm.

In our studies, if the patients have a Glasgow coma scale score of nine or more, so that

includes some patients who are not all there, but if they are hypotensive, and they have a Glasgow coma scale of nine or more, they have a 95 percent chance of surviving. So, if you introduce something else, if you think you are going to improve on 95 percent, you are just not going to do it, because the problem with these studies, the trauma studies, as has been said, and I=ll just say it again, the patients fall into three categories. They are going to be -- the largest group of patients that would be entered into the study are going to survive no matter what you do, no matter how inept you are as a surgeon, no matter how poor your pre-hospital care may be, the great majority of patients are going to do fine, they are going to survive.

There=s going to be a minority of patients who are going to die no matter what you do, no matter how great a surgeon you are, no matter how good your emergency department is, and so on, they are going to die.

So, the only patients that you have a chance of making a difference is going to be that intermediate group. If you exclude the patients with head injuries you are going to be dealing with a group of patients in whom it=s going to be very difficult to

improve upon current therapy, so that=s why I think that the head injury is the key in all of this. If not the head injury, the low Glasgow coma scale score, keeping in mind that a lot of the patients who have Glasgow coma scale scores that are low actually won=t have a head injury. In fact, about half of them won=t. But, even so, that identifies the patients who are likely to die, and those are the patients you can help. In fact, it may be that some of these solutions have their greatest potential in the patients who had the low Glasgow coma scale scores, who had it on the basis of shock, and the low score just indicated the very virulent in-stage form of shock, and that=s the patient that you want to do something different on.

DR. WEISKOPF: No, I would agree with that. What I was trying to exclude, Jim, were the patients with direct head injury because it=s hard -- well, it=s not -- one, would not necessarily a priori believe that this sort of therapy would have an impact upon that, and that would be biasing the results.

DR. HOLCROFT: No, I=m just saying that actually this is the group of patients that you can help. We already have, we might as well say we already have a lot of experience with hypertonic saline in these patients, and in those studies, every study

that=s been done on that has shown an improvement in survival, and in some of the studies it=s been twice, that is, the survival rates have doubled in those patients. And, the reason why there=s potential for the patients with the head injuries, and why I don=t think we should say it=s hopeless, is because the patients suffer a direct injury initially. That you can=t do anything about. But then, they have edema around the area, hemorrhage around the area, if they are hypotensive from a ruptured spleen or some other injury, if they are hypoxemic because their respiratory drive is lowered, then those things add up and that will convert brain that=s kind of on the margins into dead brain.

And so, there is hope, I think, in some of those patients, keeping in mind the point that Doctor Joyner made, that you=ve got to make sure that your new agent doesn=t make things worse by having an adverse effect on oxygen reactive species, or having an adverse effect on extravasation into the brain of a potentially noxious material or something, so that=s why you have to have the endpoint of mortality.

But, there is hope for some of those patients with head injuries. I=ve got to believe that. If you don=t believe that, then there=s not much hope

for changing much of anything we do, because that=s where the deaths are.

DR. CARSON: If I might change the commentary just slightly, it=s obvious mortality is important, but we need to look at morbidity events as well. And so, I don=t think any of us are implying that it=s mortality alone. Clearly, you want the total clinical picture, which would include infections, and ARDS, and, you know, renal failure, all the kind of traditional outcomes that occur in this environment would be very important to evaluate as well in the composite evaluation of these drugs.

And, if you don=t show mortality differences, but you show some of these other outcomes are affected, that would be really important as well.

It=s Carson -- you are looking -- I moved, sorry about that. I=m just seeing if you are paying attention. Okay.

CHAIRPERSON FITZPATRICK: Given those parameters, what I also heard yesterday was that the panel would be willing to accept a less than Astatistical@ significance or a statistically powered study, if it was impossible to obtain the number of patients required to get the statistical power you would want, and that=s the last comment.

There is some -- there=s a relative degree of comfort with a less than truly statistically significant result, given clinical parameters.

DR. JOYNER: I would agree with that, especially in the context of the fact that our current transfusion practices are based primarily on issues which could be described as our own clinical comfort.

DR. KRUSKALL: I hate to tread on statistics, because it=s so dangerous and Jeff will hit me, but --

DR. CARSON: I=ll have to move again.

DR. KRUSKALL: -- I don=t think the power has to be as strong as we=ve ascribed, and I think the Baxter trial has a lot to teach us. This was a trial with increased mortality, it was not a 64,000 subject trial, and the mortality did not come out of the blue. It had corollaries in terms of the serious adverse events and the adverse events which mirrored the problems that contributed to the mortality. So, I think that the biological power can be done with fewer subjects, provided that you can look at both morbidity and mortality and make sense of them as you interpret the data.

DR. NESS: Yes, and the other caveat I think for that, your Phase III study can be smaller and,

perhaps, not statistically significant if you=ve taken a product to it, which in all the preclinical and early phase clinical stuff appears to be relatively innocuous and bland. It doesn=t have any hints of toxicity, so I think that=s a big caveat for determining the final size of your ultimate study.

DR. CARSON: Since my name has been used in vain, I=ll -- see, I completely agree with the common sense issue. The way you characterize it statistically is, you are just willing to accept, you define equivalence with broader criteria, so that, you know, if you require 15 percent versus 15.5 percent, which is where that 64,000 patient number, you know, that=s equivalence to a level of precision which none of us think is reasonable.

If you define precision as plus or minus five percent then you begin to get into a number that starts to become achievable, maybe it=s still not achievable, maybe it needs to be a little bit wider, but I think you can define it, you just need to apply common sense to this in terms of what are clinically important differences that you are willing to miss.

CHAIRPERSON FITZPATRICK: Just to clarify, these are my really quick takes, and the reason I have them up there is just so that we get these points made,

and that they go in the record for the transcript.

As we go on through hemorrhage and hemorrhagic shock, a point has been made by several members to include head injuries to increase the number of included patients, to be able to clearly see the difference in survival. A question of safety has been raised several times in head injury, head trauma patients, and that it clearly has to be defined that the product would be safe for those patients in order to include them.

Efficacy markers have been discussed a number of times, and what is efficacy of this product. To simplify, does it carry and deliver oxygen and is it safe, and is the mortality a factor, and other than mortality should you have other factors for efficacy, such as lactate, base excess, in vitro parameters, and other clinical things to look at that could give you a sense of efficacy or define it.

Any comments on those?

DR. HOLCROFT: You=ve already heard me about the lactate business. My problem with the lactate is the following. First, I don=t think it=s been confirmed that definitively, and if it has been then we should be able to duplicate it in the study, that=s number one.

Number two, is some of the patients who

have suffered the most severe injuries, when they arrive in the emergency department as an example, will have fairly normal lactates, or lactic acids, and will have fairly normal base deficits, and the reason for that is they=ve got all these evil humors out there in their periphery, including hydrogen ion, that=s just hanging around there, and there=s no perfusion. Once you resuscitate them, then the hydrogen ion and what not comes back into the central circulation where you measure the actual value.

So, that=s a major problem with using some of these surrogate endpoints, such as the ones you mentioned, lactic acid and the base excess and so on, or deficit in base excess.

So, I wouldn=t accept those, and I wouldn=t even accept them at 24 hours, because if we knew for sure what the endpoints were we would -- well, let=s say it this way -- I just don=t think any of us really can agree on what the endpoints for resuscitation are. I bet if you went down this panel I bet you=d get different opinions about even something as straightforward as blood pressure, something that=s been measured now for 100 years in patients, and I bet we couldn=t even agree on that as a group, much less agree on something like this.

So, I think we should look at those things, they would be of interest, but I sure wouldn=t use it as a surrogate endpoint, or use it in making decisions about whether to license a product for this particular indication.

DR. COHN: I agree.

CHAIRPERSON FITZPATRICK: Okay.

One of the comments during the Baxter trial, and one of the comments when we were discussing statistical sampling, was that by ending the trial early you defeat the purpose of the statistical sampling. So, I took from that that to conduct a study to its conclusion, if at all possible, and understanding that you are not putting patients at risk, because canceling early can negate the power of the sampling, we also discussed that the Apache scoring system had inherent difficulties and flaws and might not be the best tool to use for inclusion/exclusion, but there could be a subset of indicators, such as Doctor Holcroft suggested, that were simpler and might be able to be used.

DR. COHN: The only thing I was going to say was that, there is probably -- it=s probably reasonable to exclude patients who you feel are not going to survive 24 hours, and at the extremes of the Apache

score, you know, Apache greater than 30, that seems to be a reasonable extreme that would identify patients that are likely to not survive. You may decide not to do that, but to admit patients into a trial such as this, where you feel that they are certain to die, you know, the person with a transcranial gunshot wound and a blood pressure of 40, you know, that would probably not be reasonable, that=s all I was going to say.

DR. WEISKOPF: I have to take substantial issue with the first bullet. Studies are designed for certain power based on a null hypothesis, that is, that the treatment arm will not differ from the control arm.

The entire purpose of the Data Safety Monitoring Board is to look at the data to ensure that we are doing -- or the study, the drug, whatever it is, is doing no harm.

That stems from the fact that the hypothesis may be wrong, that the purpose of doing the study, one of the purposes is, you don=t know what the effect is going to be, and if it turns out that the effect is different from what one anticipates, that=s the purpose of the Data Safety Monitoring Board, to step in and say, well, despite everybody=s best intentions this isn=t working out, we are doing harm, stop it.

DR. KRUSKALL: Yeah, and it seems to me that there are very clear-cut statistical tools for determining that, in terms of early stopping rules and boundaries, and to me this would be a very black and white thing, and we should take that bullet out.

DR. CARSON: Since I=m probably the source of that bullet, I don=t agree with it. I agree with -- you know, the Baxter trial had a huge difference that you couldn=t make go away, that when you set up stopping rules the statistical criteria for stopping rules earlier are more rigorous than -- they are not .05, they are much, much more rigorous. There are certain standard time periods that you look at data, and the p value required is much larger -- I mean, much smaller than you traditionally use.

So, I don=t want -- I think that should be removed. That=s not the point I was trying to make. It may very well be that there was bad luck in this, that there were small numbers and randomization didn=t work, and all those other issues that, you know, could explain why you got burned with this small trial, but you can=t look at that big mortality difference that exists in the Baxter trial and ethically let it go forward. I would never have. So --

DR. JOYNER: I=d like to take small

exception with that, and that is, I think you have to, before you cancel anything, I think you have to look at this, you know, the folks from Baxter believe that the luck of the draw was working against them for whatever reason. And, I think studies should be canceled on the basis of what the Data Safety Monitoring Board says, provided people are adequately convinced that you just did -- that=s why you do large trials, as you pointed out many times, so that heterogeneity comes out in the wash. And, if your first 50 or 100 patients in each arm are really different, then I think it=s incumbent on people to have some discipline, as difficult as it, because I think any time you step away, and we=ve talked about whether these things should be approved and let people, you know, rely on post-marketing surveys and so on and so forth, but I think any time you step away from these disciplined randomized trials you are asking for trouble.

DR. KRUSKALL: And see, I don=t agree with that. I think the issue isn=t do you stop when you hit the boundaries, it=s do you stop before you hit the boundaries. I think that=s, perhaps, what this bullet was talking about, in other words, do you get cold feet as you are getting close to a stopping rule.

And, maybe what the spirit you were trying

to capture was, adhere to the rules and don=t stop until you get to the boundary. But, I don=t know that it=s really necessary to say that, and I think it would be foolhardy to continue after you=ve crossed over those boundaries.

DR. CARSON: I wouldn=t stop if you are not at those boundaries. Those boundaries are set up to consider the things that were raised here, and to recognize that you are going to see these variations in small numbers, and to protect against stopping prematurely, that=s why they are set up that way.

CHAIRPERSON FITZPATRICK: Thank you.

In the face of a trauma trial, there was a lot of discussion about resuscitation and the impact that could have, along with all the other complicating factors, and the Baxter study may have been better than we thought, that we just may not have liked the answer.

Can equivalence be a basis for licensure? At some points, the panel seemed to say yes, and make it simple. What I=m going to ask the panel to do during this session is consider what they said this morning about the clinical and preclinical trials and the number of parameters they looked at as needing exploration and data collection in those trials, versus what they said yesterday about the equivalence basis,

and saying that, yes, we need the trials, but make them simple. We can=t answer all the questions with one study. Power is difficult, back to the common sense versus statistics argument, and that the inclusion/exclusion criteria need to be examined. There=s going to be some redundancy as we go through here, because there was redundancy. We talked about several things throughout yesterday and this morning. But, is there a conflict between what you said this morning and what you said yesterday?

DR. CARSON: In every study there=s a compromise between how much data you collect and resources and practicality, and the questions that you want to answer. But, I still think you can answer most of the general safety issues that we=ve raised this morning with a modest amount of data collection. It does not have to be super long to do that. I still think you can do it with, you know, two or three pages of outcome information, and keep the actual process pretty simple.

I mean, I=m quite sure that you can do that, and I=d be happy to share, you know, some data collection instruments that we=ve developed for other trials that look at a lot of these kinds of outcomes, and they are short, and they are sweet, but they get --

they are using validated measures, but, you know, they are collecting limited information.

I mean, as an example, if you could collect every bacterial infection that you wanted to, you know, but it turns out, at least in some of the settings that I=m interested in studying, that 90 percent of the infections are pneumonia, so I don=t collect UTIs because they are common and generally not that important, but I measure all my pneumonias. And, I give up some of those other ones because they are not as important.

So, I think if you are selective and thoughtful about it you can -- you=ll start with a very long list, and then as you start calculating rates and so forth you can try to cut it down.

Now, the problem with that is that you are very interested in rare adverse effects here, because you are still looking at low rates, and so there=s going to be a compromise, and, you know, I don=t know that I understand what that compromise is yet, but it does not need to be a 100 page data collection instrument, even to get some of those relatively uncommon things, I think.

DR. NESS: Well, I somewhat agree, but somewhat don=t agree. I=m a little concerned that when

you talk about doing something which is sort of quick and dirty it=s always dirty and often not so quick, in terms of separating out what you end up with. So, I=m not sure that I wouldn=t rather have a smaller study of very well-studied patients than a larger study where I don=t really know what I=m collecting.

DR. CARSON: It does not have to be dirty. They are never quick. There=s not a study I=ve ever been involved with that=s ever quick. They are always painful, but you still can keep your data collection limited. It=s a limited data collection.

DR. JOYNER: I think these responses reflect -- I think one thing there is consensus on is that this is a very, very difficult issue to study in the trauma patients, in a difficult group of patients, difficult environment to study, and these are really hard things to do. This isn=t like getting any of the anti-hypertensive or cholesterol-lowering drugs approved. So, I think a lot of that reflects this, and it also reflects kind of the bimodal distribution of the types of studies we=ve been talking about.

One is a trauma study where there=s going to be high mortality, and you really have nothing to offer these patients, and everybody is anxious to do something that makes things even a little bit better,

versus use in elective surgery where we have, the current therapy is pretty good.

So, I see this as really, you know, how do we -- how does industry work with the FDA to design reasonable trials about a very difficult product given to sick patients under the most trying data collection circumstances you can imagine, as opposed to some of the specifics you could agree or disagree with, but I think everybody would agree with those. And, that=s the real challenge in all this, if you ask me.

DR. COHN: Personally, I think that the safety trial or the licensure trial should be the general surgical or, not general, the elective surgical trial, to get an adequate number, to study them in great detail, to convince us to whatever degree that this is safe, and then that things like trauma trials, which will be difficult to perform and could be very easily left to Phase IV trials, I think could happen after licensure occurred.

I don=t believe that there is going to be a high abuse rate in the trauma field, because I think that the trauma directors who take care of the great majority of the trauma patients will want to study this before they just blanketly use it, and I don=t think any of us would stand up here and say that we are just

going to apply something without any data whatsoever. That is both expensive and potentially harmful to our patients in the pre-hospital area, that we=d want to do a Phase IV trial. But, I don=t think that that=s the ideal way to answer safety questions, because I think there=s just too much noise. I think it=s sort of the equivalent of trying to study this in liver transplant patients. I just don=t think that we can answer safety data in liver transplants when everybody has an adverse effect, you know.

CHAIRPERSON FITZPATRICK: Okay.

One of the comments yesterday was to include all patients in hemorrhagic shock, including head trauma, and we discussed that.

There was a lot of debate about concurrent control. Doctor Gould felt very strongly that that could be construed as not providing therapy to a patient that needed it, not providing beneficial therapy to a patient that could benefit from a product, versus the clinical arguments of having concurrent controls.

The question is, if we got to a safety point would a full-blown study answer this question? In other words, just product versus just red cells, and if mortality is the endpoint could you establish

equivalency based on a study like that?

DR. HOLCROFT: It seems to me, are we talking about the elective surgery case or the trauma case, and that to me is where everything -- I just make a clear distinction in my own mind. So, if this is trauma, then I say absolutely, this has to be a double-blinded control, absolutely, no question whatsoever.

And, I would also say you should collect a lot of data on those patients, because if, indeed, this stuff is going to save lives you=ll be able to demonstrate it with a relatively small number of patients, and it will be possible to do the study, collect a lot of data, and you=ll be able to do a good Cox proportional hazards analysis or some sort of analysis to look at potentially confounding covariables.

So, I would say in the trauma case, if that=s what we are talking about right now, absolutely, you have to have concurrent controls, and it has to be double blinded, too.

CHAIRPERSON FITZPATRICK: Okay.

DR. HOLCROFT: At least in my opinion.

Now, with respect to an ER trial, I suspect the ER trial is kind of neither fish nor fowl. It=s highly unlikely we are going to have any benefit from

using those solutions in the emergency department. After all, I mean, the goal in the trauma patient is not to transfuse them at all in the emergency department. I mean, when we transfuse somebody in the emergency department, we regard that, at least initially, as a failure, or saying it another way, if the patient needs blood we figure they should have been in the operating room, and then we review the video tapes and we say, how come. You are giving this patient blood, and meanwhile he=s just bleeding out from his spleen. You can give a lot of blood that way, you know, that=s not the treatment for a ruptured spleen.

So, that=s the problem with the emergency room trial. I don=t think this product is likely to be any better than what we already have, so it=s neither fish nor fowl in that regard, and then it=s neither fish nor fowl in terms of safety, because there are all kinds of things going on in the emergency department that just confuse all of us. It=s just hard to study.

So, you don=t really get good safety data out of those studies either. So, I would speak against doing ER trials. It seems to me you do it one way or you do it the other way.

CHAIRPERSON FITZPATRICK: If equivalency is

a requirement for licensure, and we have to have power trials, one of the questions raised was, will we ever see a licensed product if equivalence is the endpoint? Can you do an appropriate trial for equivalence? And, we've discussed that allogeneic transfusion may not be a very good surrogate endpoint.

DR. CARSON: The answer is yes you can do an equivalence trial, but you just have to be --

CHAIRPERSON FITZPATRICK: Doctor Holcroft has to leave, so any further comments?

DR. HOLCROFT: I've said more than enough.

CHAIRPERSON FITZPATRICK: Okay.

Thank you very much.

DR. HOLCROFT: I learned a great deal, this was very educational.

CHAIRPERSON FITZPATRICK: Thank you.

I'm sorry.

DR. CARSON: -- it's an identical comment to a few slides ago. You can do an equivalence trial, you just have to be -- how you define equivalence needs to be, perhaps, defined a little more broadly in this situation.

CHAIRPERSON FITZPATRICK: Going back to the acceptance of the level of risk.

DR. CARSON: Right. You know, you can

define equivalence as 0.5 percent, you can define it as five percent equivalent, or ten percent, and your sample size is driven by how small a difference you want to consider equivalent.

CHAIRPERSON FITZPATRICK: I think one of the questions the FDA wanted us to consider was what would you, as a panel, be comfortable with in defining? Would you be comfortable with five percent, or would you require the .5 percent?

DR. WEISKOPF: You=re talking about equivalence of adverse effects?

CHAIRPERSON FITZPATRICK: Yes, and there=s a range been given there, 0.5 to five, there was a lot of discussion about safety of red cells versus this compound, and there was discussion about different patient groups. You=d be willing to accept a higher risk in one patient group versus another patient group. Is there a way to bring that together?

DR. VLAHAKES: I think it has to be cast as a percentage of what the baseline risk is, and that baseline risk may vary over ten to one. So, if you wanted to say ten percent of base -- make it ten percent of the baseline risk, or five percent of the baseline risk, that might be a better way to sort of organize the study.

DR. CARSON: So, we=re really contrasting two concepts. One is what=s called a relative risk reduction, which is a percent, you know, this drug reduced mortality by 25 percent, but the absolute risk reduction is the difference between the two groups. And, if we use the example from yesterday, 15 percent was the baseline, and 20 percent with the other group, there would be a five percent absolute risk reduction. So, it depends on which number we are talking about. I think what Gus is suggesting is thinking about in relative risk reduction a percentage.

CHAIRPERSON FITZPATRICK: Most of the discussion seemed to revolve around absolute risk, and what I heard today was that that=s going to depend on the patient group that the product is going to be used in.

DR. WEISKOPF: That=s compounded by the issue of how well are we going to know that risk, and we haven=t got our arms around that answer either.

DR. CARSON: Yes, but every sample size that you ever do is, you know, you are going to look at the numbers, you are going to look at what=s achievable, what=s realistic, there=s a lot of judgment that goes into these things, and I don=t want to give a number, because I think that number might trap people into

unachievable goals that aren=t in the interest of our patients.

And you have to look at these individually and have to -- you know, it depends on what the rates turn out to be, it depends on, you know, what=s achievable. There are a lot of issues that go into sort of deciding on a basic number, and I think it=s a bad idea to have us suggest a number that you think it=s held to. I wouldn=t do that.

DR. JOYNER: I think it will be different if you are talking about the trauma trial than an elective surgery trial. Just basically what we are saying, I think that also has to be balanced with the fact that the $64,000.00 slide, the 64,000 patient slide of Doctor Gould, and the fact that these types of trials, all drug trials are costly, but these are going to be particularly costly, due to the nature of the data collection, where it is going to be collected, what kind of patients are studied.

CHAIRPERSON FITZPATRICK: Doctor Klein brought in some new questions this morning about the preclinical trials and appropriate animal models. Some of the discussion there revolved around shock trauma models, anesthetized versus non-anesthetized models, primates, of the need to define the toxicities to be

addressed, the need for re-challenge for immunogenicity studies.

While the panel was asked about three or four common models, it seemed apparent that there didn=t seem to be a way to come to grasp with three to four common models for the product. Does that seem reasonable? I see a frown.

DR. WEISKOPF: I=m not sure we can mandate specific preclinical trials based on the current level of knowledge.

Furthermore, I am uncomfortable with mandating trials in primates, unless somebody can show that the data collected from primates can be collected no other place, which is what frequently IRBs demand in any event, because primates are so difficult to obtain and to work with. I don=t see that particular need.

CHAIRPERSON FITZPATRICK: Along those same lines, there was discussion about the need for controlled and uncontrolled hemorrhage models, and looking at other potential toxicities, neurotoxicity, the Glasgow outcomes, scores, stroke and others. Does anyone have specifics they=d like to add to that?

DR. JOYNER: I=d just like to reiterate the need to, at least for the elective surgery type trials, to study these in potentially or at least address some

common co-existing diseases associated with aging, because older people are going to get these, which would mainly be hypertension, subclinical renal disorders and reduced ejection fractions in potentially pulmonary disease. I think those would be the four big ones. And, to the extent you wanted to study maybe diabetes as well. I think those are the five biggies with aging.

DR. VLAHAKES: And, I=d include in the list this silent atherosclerosis.

DR. JOYNER: Yes.

DR. NESS: One of the issues in trauma that I=ve been thinking about, I=m not sure how the FDA or anybody can deal with this, but a high percentage of the trauma, potential trauma recipients, will cease to be patients and become organ donors. Are there any studies, or is this an issue that we need to deal with in terms of if there is a toxicity, vasoconstrictive effect in giving this terminally, for example, would that make organ harvesting worse?

DR. VLAHAKES: I don=t think that will be an issue, because these are going to be cleared and your end drugging system tests to qualify them for donation will be done. The time from the termination of therapy to the trauma patient until the time of organ donation

is sufficient time, I think, for that to occur, at least based on what happens in New England.

CHAIRPERSON FITZPATRICK: That raises another point, Doctor Ness, that hasn=t really been considered before.

DR. COHN: Right. The fact is the majority of people who are our organ donors, and there aren=t all that many of them, are folks with devastating head injuries that we might possibly be able to identify very early on as someone who is not a good candidate for the study. You know, the person with brain coming out of the side of their head is not a good person to be putting in this, and even though they might survive 12 hours to become an organ donor they generally are identifiable. I mean, there are some patients who definitely could get this and two days later herniate and I think it=s a reasonable question, but I think it won=t be commonly encountered.

DR. WEISKOPF: Unless my right and left ears are connected to two different brains, I thought I heard arguments earlier this morning to include all those patients in the trial.

DR. COHN: I=m sorry, we shouldn=t include patients who have -- who are unlikely to survive 24 hours. That=s what I was saying. The patient that

comes in that has got evidence of a devastating brain injury, such as the one with brain extruding, okay, or the one who is herniating in front of you and goes to CAT scan and is going to be let go, that person I wouldn=t include. The rest of them I would.

DR. WEISKOPF: Well, I understand, that=s what I was trying to say earlier but, perhaps, not in as elegant a manner, but what I thought I heard Jim say was that, no, the neurologically injured patients, the majority of those will be helped.

DR. COHN: What he was saying was that people with a GCS less than nine, even the ones with a brain injury, there are folks -- he also said that there is a population that we cannot help, that=s what I=m saying, recognizing that, you know, we only understand a certain small percentage of those, but there are a bunch of people with a fairly significant head injury who may benefit because their penumbra, the area that can go either way, may benefit from this.

What I=m saying is that most of the people who are organ donors, or some of them, may come in and be actually sort of not included in the trial because we look at them and say, there ain=t no way this guy is going to make it 24 hours.

DR. NESS: Leaving aside the issues of the

trial, I think one of the questions that you could ask is, would this make a potential organ donor worse or even make it better for the organ recipient further on to have better perfusion early on.

CHAIRPERSON FITZPATRICK: That is a possibility.

In discussing the linkage, a number of measurement parameters were discussed in the models. That=s the listing that I got trying to take quick notes. I=m sure the transcript will maybe have a few more, but we had myocardial injury, ischemia, renal toxicity, liver damage, pancreatitis, muscle injury, nausea, vomiting, GI distress, perhaps, inclusion of animal models with co-existing disease, multiple organ failure.

DR. CARSON: Add pulmonary.

CHAIRPERSON FITZPATRICK: Okay.

DR. WEISKOPF: Neurologic.

CHAIRPERSON FITZPATRICK: That=s another one.

One of the other questions was, shouldn=t oxygen therapeutic be evaluated in a perioperative setting in high-risk patients? I think that=s what we ended up modifying that question. I got from the panel that controlled clinical trials are necessary, and that

a high-risk patient population would be required to see large volumes used, that there is a difference between a euvolemic stable patient versus a hypovolemic Aunstable≅ patient, knowing that the goal of surgery is to keep all patients stable throughout the entire process, that we have different risk acceptance for different patient need groups, that high-volume procedures, this is my own comment, you could have a pre-consent for a patient going to a procedure that might be a high-volume or high-risk procedure, that should it become necessary they could be pre-consented to use this product, be enrolled in the study that way. Trauma, in some panel members= opinions, provided the best patient group for high-volume studies, but we need controlled studies on safety and toxicity before we can go to the trauma studies and use it on high-volume patients in trauma, because of the heterogeneity problems, because of trying to sort out what's the toxicity, what contributed to mortality, what didn=t, how did the product affect the outcome.

DR. WEISKOPF: I almost hesitate to bring this up, with only 35 minutes left to this conference, but the risks that we have been talking about for a day and a half, we haven=t addressed the issue as to whether these risks are dose related or not dose

related. And, for the ones that are dose related, do we need to talk about studies with respect to what dose level is required to be looking for those toxicities?

CHAIRPERSON FITZPATRICK: Do you want to comment on that, Doctor Silverman, since you had some comments to that yesterday.

DR. SILVERMAN: Toby Silverman, FDA.

We=ve always said that the purpose of a dose escalation study is to look at maximum tolerated dose. You absolutely must know the parameters in which you are working. For trauma, I think you really would like to have a product where you can go, no holds barred, and you really would like to know if you can do that.

DR. WEISKOPF: Sure, I understand, but ordinarily dose escalation studies are not -- we are talking about just a pure dose escalation study as opposed to a Phase III clinical trial, those dose escalation studies generally are relative compared to the Phase III clinical trial, are much smaller populations. What I=m asking, I guess, is are there specific doses that we ought to be -- that need to be looked at in the Phase III trial that will be accumulating these sort of toxicity data.

DR. SILVERMAN: That=s a very difficult

question. I think that the answer to that is yes, you want to go, you want to confirm your maximum tolerated dose from the Phase II, and you do want to be looking for any additional rare toxicities at the highest doses, so we will be looking. If you ask for a label that goes to 30 units, we are going to want to see a certain amount of data, you know, in a sizeable number of patients at that dose level. How could I write a label that says you can administer to the putative 30 units if I don=t have the information.

CHAIRPERSON FITZPATRICK: Other patient groups that we looked at were commented on as being potential for high volume or high risk for aortic aneurysms. Redo CABGs, the warm autoimmune hemolytic anemia, sickle cell, the ideas for entry of patient groups into studies to look at these parameters.

The potential of off-label use was discussed, the FDA said when predictable it should be studied. The panel seemed to agree with that comment, and went back to the trauma victims and Doctor Holcroft=s comments about inclusion of those patients.

Trial design is one of the topics we are supposed to get through this morning. We discussed that throughout the conference. My understanding of what we heard was that additional trials in a

controlled study at large doses are needed before conducting a full-blown trauma trial to assure safety. Dose limiting was just discussed. One of the questions would be, is there a dose limit that the panel would consider before going to a trauma trial, ten units, 15 units, what would be a parameter in that dose escalation study that would give you confidence to use it in a trauma trial.

DR. KRUSKALL: Well, there=s a rationale to ten units, because it represents a blood volume, a definition of massive transfusion. The problem that I have is imagining getting an elective surgical trial in which we get up to those doses, so I think practically we are not going to be able to get to that level before we move to a trauma trial.

DR. CARSON: But, I thought that there was a consensus towards the end of the discussion that a trauma trial should be the first place to go for data to establish efficacy, and that treatment and that safety, some safety information would result from that, because, I mean, Jim=s point was that the place that these drugs are most likely to really affect outcome is in those kinds of cases, and are much less likely to affect outcome in an elective setting, and that, you know, he had talked about originally the concept of

proving safety in elective settings and then bringing it to a trauma setting, and I think -- I thought we got to the point where there was a sense that, the trauma setting is where we can really affect outcome, let=s go and figure out if it works in that setting and begin to assess safety=s part of that process, and not to put it off until later. At least that=s what I came away with, maybe I=m in the minority on that one.

DR. KRUSKALL: It=s probably where any residual semblance of consensus disappears, but I think that our hands are all tied because we can=t do -- or I=m told we can=t do two studies, that we have to focus on one. And, as tempting as it is to follow Willie Sutton=s law and go for the money, because I think that the efficacy and the utility of this, these materials, are going to be in trauma, trying to decipher safety and efficacy is going to be so challenging that I thought we were headed toward an elective surgical trial to at least get a handle on safety, so that we had, to the limits that we could, in terms of the volumes that we would have liked to have seen, some idea of safety that we then translated to trauma trials, perhaps, in a Phase IV trial.

DR. COHN: I think paraphrasing Jim=s comment that he would be uncomfortable doing any kind

of a waiver of consent, or a pre-hospital, or a trauma trial where consent would be highly difficult to obtain he=d be uncomfortable doing that unless the preparation appeared to be at least safe in some volume.

CHAIRPERSON FITZPATRICK: That was one of his comments to me before he left also.

DR. WEISKOPF: And, I think as a practical matter, if any sponsor is going to conduct a large-scale elective surgery safety trial, they will also power it for efficacy as well, so they are likely to do both simultaneously.

CHAIRPERSON FITZPATRICK: Doctor Vlahakes.

DR. VLAHAKES: No, I was going to comment about the discussions, recall that we did have differences of opinion, it did go back and forth.

CHAIRPERSON FITZPATRICK: Okay.

Another issue was that if we get -- when and if we get to the point of a trauma trial, it should be conducted in an all or none format.

DR. KRUSKALL: I hate to make us go back, but assuming that we do this surgical trial and we get satisfactory safety, but can=t prove efficacy, do we hamper ourselves in any way in terms of the need to go on to a trauma trial by virtue of the fact that this may not get licensed? What dilemma do we face if we

show that we have a safe material, but that it is not efficacious? Is equivalent enough to get it licensed then at that point?

CHAIRPERSON FITZPATRICK: I have to defer to the FDA on that.

DR. KRUSKALL: If we conduct these surgical trials, large trials, safety is assured, but the material is not shown to be efficacious, equivalent to or, perhaps, barely equivalent to blood. No blood is saved, I guess is our endpoint. Is the product not licensable, and what does that do to our interest in doing this for trauma?

DR. AEBERSOLD: The Phase III trials that have been described use reduction or avoidance of allogeneic blood as a surrogate endpoint. If one doesn=t accomplish that goal, I mean, and many members on the panel even questioned whether that is a measure of efficacy at all or can be achieved, because blood is very safe, if you don=t at least avoid or reduce allogeneic blood what have you done? I mean, why would you use this product if -- I mean, the FDA has always, in our discussions with sponsors, pointed out if all you do with a short half-life product is delay the allogeneic blood you might as well give the allogeneic blood up first. We have heard no reason not to do

that, and I just want to point out that even though some of the questions were framed as if one is doing, a manufacturer is doing a single pivotal trial, that=s not to suggest that that would be what FDA would prefer.

I think it=s very clear from the discussion that there=s potential for use on both ends of the scale, and different questions on both ends of the scale, and would we prefer that a company do a trauma trial and a surgery trial? Yes, I think we would, that=s what Baxter was doing.

DR. KRUSKALL: All right, that was really what I was getting at, because if we are preordained to suggest one trial, we actually slow ourselves down if the surgical trial does not produce data that allows a marketable product.

DR. WEISKOPF: I certainly understand your point about the need to demonstrate efficacy. That=s, I suppose, a given, with the possible exception, and we=ve talked about it in the issue of trauma and in other circumstances, but it=s broader in scope, and that is availability. We=ve talked about specific isolated circumstances, but what about if we reach the point next year, which was predicted by the NIH meeting earlier this year, that there is not going to be just

spotty shortages of blood, but we will have a national chronic shortage of blood. I=m not proposing an answer here, just suggesting that the problem is a little more complex.

DR. AEBERSOLD: I have the same response for surgery. If all you do is delay the need for allogeneic blood, and you are giving the same amount of allogeneic blood, you are not helping a shortage at all. As a matter of fact, you are making it worse because there may be some competition for human blood derived blood substitutes. This is all outdated blood right now, but if you don=t reduce the amount of allogeneic blood used, you are not helping the shortage either.

DR. JOYNER: A surgical trial may be a little different, though, than a trauma trial, where you, to use Doctor Cohn=s phrase, you are using it as a bridge to transfusion in places where you can=t give blood, a helicopter, out in the field, whatever.

DR. WEISKOPF: Unless -- sorry.

DR. JOYNER: So, that would be -- so, the bridge to transfusion idea versus not in a controlled hospital base, showing that you give a couple units during surgery and have to give a couple more later, versus just giving a couple, a couple of units of RBCs

up front. I think that=s a separate issue.

DR. AEBERSOLD: Yes, I agree it=s a separate issue, I was addressing my comments to the question about in elective surgery, if one didn=t show an avoidance or reduction of allogeneic blood.

Clearly, in a trauma setting, I think that my take is that everybody on the panel thinks that there=s some patients who would potentially be saved in the transport setting of having an oxygen carrier available, although I think I also heard it would be very difficult to conduct a clinical trial, not impossible, though.

DR. WEISKOPF: Your second bullet point I think is not possible, given the current half life of the compounds that we heard about, which range from some hours to a day or so, dose dependent, but in that range, that eventually those patients will need, if you are talking about substantial hemorrhage, substantial blood loss in the trauma patients, they will need something following once the product dissipates. So, I don=t think it=s going to possible to a priori in advance, have a prospective randomized study, in which you would expect one arm to be completely transfusion of ordinary blood components free.

DR. VLAHAKES: I think the discussions that

were taking place on that point yesterday centered around this definition of stable, and stable means when the surgical bleeding is controlled in the operating room and the turnover of blood volume, rapid turnover of blood volume from surgical loss ceases.

CHAIRPERSON FITZPATRICK: There were comments to that effect, and also to a time limit, say 12 hours, 24 hours. There were a variety of comments as to what comprised that period of providing the oxygen carrier versus red cells, knowing that the patient at some time might need to be weaned to red cells and that factored in.

DR. CARSON: But, the principle is that someone comes in with a vessel that=s cut, someone is bleeding like crazy, that at that time you are using the blood substitute to see that patient through. Once hemostasis is established then you are going to typically want to go to allogeneic blood then, because these drugs don=t hang around long enough for that. So, it=s kind of following the bridging concept that seems like the ideal way to use these drugs.

CHAIRPERSON FITZPATRICK: But surpassing the ten or 20 unit limit in the study that is currently set, allowing them to go beyond that.

DR. CARSON: Yes. I mean, that=s just

common sense.

CHAIRPERSON FITZPATRICK: Comments were made that rather than being spread over 18 centers for control purposes, and data collection might be better to look at four or five high-volume trauma centers. There was continued concern over dosage, which has been discussed today, complications that result from patients receiving both an oxygen carrier and red cells that need to be factored into the trial design or factored out of the trial design.

DR. CARSON: The number of centers you need is going to be determined by the sample size. You know, clearly, you are better off dealing with fewer centers with higher volumes if you can meet your recruitment needs. That may not be possible for five, and you just -- you know, you need to build into these trials really, really careful quality control, and training, and piloting, and, you know, you maybe want to start it in a few centers, figure out how to do the study right, get through your, you know, figure out all the pitfalls and work them out, and, you know, then expand the number of centers that you need to meet your recruitment needs.

But, there=s a lot of experience throughout the world in doing multi-center trials. The key is to

get the protocol right, make it, you know, figure out the logistics, train people really well, monitor them really well. You know, so big multi-center trials have done many, many, many times, you just need to do them real carefully and step them in.

DR. JOYNER: Could I suggest, I agree with your comments, but I think that this, the environment and what they are trying to do here is, with the exception of maybe a few things that require cardiac catheterization, is about as hostile as you can find, and I think the data from all sorts of sources show that until people start doing 100-200 of whatever it is, you know, until you overcome the original learning curve, you are going to have deep, deep trouble. So, whether it=s four centers or 18, but the key is to have enough people at each one so that the rate of -- so that the confusion associated with adding a difficult protocol to an already hostile and confusing environment is minimized. And, that=s why, I think, again, these folks have been asked to do very difficult things with very difficult products in a very difficult environment, and anything that we can do and the FDA can do to help them just limit additional sources of confusion would be helpful.

DR. CARSON: I think the key thing that you

said was, centers that have significant volumes, so that they learn to do the studies quickly and they learn to do it well. And, if you have lots of centers that do lots of volume it will work.

I absolutely agree with you, if you have lots of centers, some of which that do small numbers, you are never going to learn the protocol well enough, you are not going to get good at it, there=s going to be lots of protocol violations, and it=s going to be a mess.

DR. JOYNER: Just based on a lot of things, but I would almost require that the centers have proof that their study coordinators have actually been involved in something like this before, because they are going to be so essential to trying to make this work.

CHAIRPERSON FITZPATRICK: On trial design also, we had discussion about trials in a remote or on ambulance setting, are they necessary, could it be done as a post-market analysis after a trauma trial? And, there was discussion, I=m not sure we got a feeling as to what -- if there was consensus what that might be.

DR. VLAHAKES: Well, I=ll put an opinion out for discussion. I think it=s a hard trial to do, consent issues, et cetera, and it might be perfect for

a post-market analysis study, the consent issue is a lot less at that time.

DR. NESS: Yes, I originally argued against the idea of doing this kind of study, because I thought the variables, in terms of care delivery, would be so confusing that you wouldn=t know what you=ve got, but in thinking about the very difficult problems with sample size and all that, to do a study in the hospital setting, emergency hospital surgery, trauma setting, where you are going to do a sort of heads up comparison between giving blood versus giving a substitute until the patient is stable, and the sample sizes and all that you need, and if that=s going to be the determinant of efficacy it may ultimately be a lot easier to determine efficacy in one of these remote settings where you are really going to do the real comparison, which is blood to no blood, because that=s a real efficacy comparison that if we are really talking about this treatment as a bridge to transfusion that=s really where I think all of us were in agreement that is the real utility, the major utility of this product.

DR. WEISKOPF: Well, I think if you do this sort of study, you=ll satisfy Jeff=s requirements about minimal data collection and then some. The amount of

data collection will approach and achieve zero.

So, if the FDA is satisfied with zero data, that will be a great study.

DR. COHN: Obviously, you=d have to be very selective if you had a group of paramedics, a select group of paramedics, say, in Life flight helicopters, who were very well trained and focused, you could gather a tremendous amount of data.

But, I just want to ask, where exactly is the large trauma trail and how do I get on it?

DR. CARSON: Dick and I can=t help but discuss these issues. See, what I=ve learned from my trauma friends here is that, it seems like this is the place where you have your best chance of showing something, and I guess, I don=t know, I=ve watched EMS groups, some on TV I recognize, I mean, they are impressive, they are good. And, you know, I think they could do this, and I don=t think they have to collect almost any data at the time that they scoop these folks off their site. And, you know, they need to get them in an ambulance, they need to stick a line in them, and they need to start infusing this stuff and transport to the hospital.

And probably all the data collection that=s necessary could happen later. And so, I don=t think

any of these studies aren=t -- they are all really hard, and I=m not sure that this is any harder than some of the other ones that we=ve been talking about. I think they are all hard, and, I mean, there=s been EMS studies done in, I guess, Seattle, which established what CPR worked, and I wouldn=t reject this, again, for those reasons.

DR. JOYNER: Somebody in our department is a medical director of the local ambulance, and they=ve collected -- and they=ve also collected work for the police department on the automated defibrillators, and the dedicated senior people who have been doing it for a while, the EMTs and so forth, have a terrific relationship with the physicians, and the nurses and staff and so forth, these people can be trained and indoctrinated to do, you know, almost anything and they=ll do it. If you give them a defined scope they=ll do it with real zeal, real zeal. I mean, you know, it=s like a dog bringing you a bone, they are so happy when they do a good job because they know you are happy.

DR. CARSON: I mean, imagine that you do this, you know, in any of the major cities, even San Francisco, and, you know, you get those hard core EMS folks that work in our major cities and you train them,

I don=t know. I don=t know if it would work, I mean, you=d have to try it, but I think every one of these trials are really hard.

DR. WEISKOPF: I agree, the study could -- you could do it, the question is, what sort of data will you have with respect to what the patient was like prior to administration of therapy. Well, there=s a lot to discuss about it, but I have difficult envisioning that you=d get the kind of information that you really would like to see prior to therapy.

DR. COHN: I mean, it=s routine for our paramedics to gather the two pieces of information that we heard that are essential. Well, one would be pulse and blood pressure, and the other would be their Glasgow coma score, just the motor component, and that they can get before anything was infused. So, we basically have time zero.

And then, the second important time point is on arrival to the emergency room, so if they can, and they do reliably give us the amount of time, we have all the dispatch times available, so we can -- I think as long as there=s not too much that you are asking, I think that in terms of data that we can get some of those essential things, and let=s face it, if you had absolutely no data, other than the blood

pressure, all right, and you just knew what the systolic blood pressure was, and they called in and they got randomized to one or the other, that might, in itself, just looking at survival to the hospital, might be different. I don=t know.

DR. VLAHAKES: The EMT person would get consent?

DR. COHN: Hum?

DR. VLAHAKES: The EMT person would get consent?

DR. COHN: No, they would have -- by definition you wouldn=t be able to get consent, you couldn=t have them ask for -- even if the person could respond, you wouldn=t want them to say, well, look, I know I should be putting you on a back board now and putting a collar on you, but I have this little study I=d like to explain, do you have five minutes?

DR. CARSON: Consent is 25 pages long, I want you to read every word and initial every page.

CHAIRPERSON KLEIN: I don=t know what you guys do, and Rochester is a small town, but when we=ve done studies in the emergency department we have like these kind of town hall meetings, and we get some sort of community-based informed consent and so on, and it=s a big process, and the lawyers are involved and so

forth.

CHAIRPERSON FITZPATRICK: I think Doctor Holcroft agreed with that concept, too. Things would have to be done without consent.

DR. COHN: To do that in Miami, we=d have to use like the Orange Bowl, you know.

CHAIRPERSON FITZPATRICK: It may be empty.

One of the other things we discussed were, and we=ve talked about these, were high-volume blood loss, high-risk patients, age stratification, randomized controls and, again, powered for the toxicities that we need to look for.

Equivalency still seems to be a question after this morning, and the question came up, do we need a benefit, should we define a benefit, or is equivalency okay without a benefit. Those parameters, I think, remain to be seen.

We are supposed to take a little time and look at recommendations for the future, and we=ve got about ten minutes left, which isn=t much time to do that, but would the panel have recommendations to the manufacturers and FDA for directions that they should go with this research in the future?

DR. CARSON: I think as Jim said, we=ve all done a lot of talking, and maybe -- it=s hard to

believe that there=s much more that we can add.

CHAIRPERSON FITZPATRICK: I think a lot has been said, and I=d like to turn it over to Abdu.

DR. ALAYASH: Well, thank you very much. I=ll be very brief. On behalf of the organizing committee, steering committee, I=d like to thank you extremely much for your help and your input. I=d like to thank the moderators and the representatives of industry for their willingness to take part, and also take part, not only in the presentation of the data, but in the actual debate.

Thank you very much, and have a safe trip.

(Whereupon, the meeting was concluded at 12:20 p.m.)

1

2

3