Biopure attempted to explain other discrepancies in adverse events in HEM-0115 by noting that there were more test subjects than control subjects with a history of cardiac disease or that total hemoglobin levels were lower in the HBOC-201 group than in control. Within the HBOC-201 cohort, however, *post hoc* stratification by the presence or absence of a history of cardiac disease showed no difference in the incidence of adverse events. Further, information provided in the NMRC briefing document addresses baseline medical histories for subjects in the two cohorts, as we will see in the next slide.

[Slide] This is taken from two tables provided in the briefing document. The slide combines two tables. The table provides information about baseline cardiovascular medical history for the HBOC-201 cohort and the RBC cohort. Biopure subset each cohort, as you have heard today, into two groups. Among the red blood cell control subjects, the subsetting was by three or fewer units of red cells received, as opposed to four or more. In the HBOC-201n group, the subsetting was by whether or not the subjects also received red blood cells. As one would expect from a clinical trial that randomized only between HBOC-201 and control, and not by these various subgroups, there was little difference among the various groups in terms of cardiovascular history.

[Slide] Finally, Biopure hypothesized that the total hemoglobin was lower in the HBOC-201 arm and that his led to an increased risk of ischemia. However, the mean 1.23-gram-per-deciliter difference between HBOC-201 and red cells in total hemoglobin for lowest recorded value probably does not explain the excess of adverse events for HBOC-201. Additionally, within the HBOC-201 cohort, stratification by nadir total hemoglobin above or below 8 g/dl revealed little difference in the incidence of high-frequency events, such as hypertension, troponin elevation, or oliguria.

[Slide] Safety conclusions: Excess adverse events are consistently associated with the use of HBOC-201, whether one looks by red blood cell-controlled surgery studies or crystalloid/colloid-controlled surgery studies, whether one stratifies by age in the surgery studies. Total hemoglobin concentration and history of heart disease do not appear to be independent predictors of adverse-event imbalances when assessed in *post hoc* stratification of the HBOC-201 cohort in HEM-0115.

FDA considers that these adverse events are important to consider when thinking about RESUS.

I would like to switch gears and talk about dosing and administration.

[Slide] The default rate of administration for

HBOC-201 in RESUS is, as you have heard, 50 mL/min, although the actual rate will be determined at the scene, according to the medical judgment of the EMS provider. The preclinical database consists predominantly of studies in hemorrhagic shock where the rate of administration ranged from gravity infusion, not otherwise specified, to 10 mL/kg/min, as you have heard. However, there were no deliberate dose-ranging studies submitted.

Similarly, there are very limited clinical data on the rate of administration. For example, in the crystalloid/colloid surgery studies, the rate of infusion was approximately 3.8 mL/min. In HEM-0115, the mean infusion rate was 5 to 5.5 mL/min, and there were only four of the 353 subjects who were administered product above 40 mL/min.

As with the preclinical situation, there were no deliberate dose-ranging studies or rate-of-administration studies.

[Slide] The limited safety data for product administration at higher dosing rates and doses is a principal concern, given the known intrinsic properties of HBOCs -- that is to say, vasoactivity and vascular injury -- and the adverse-event profile of HBOC-201 in previous trials.

Now I would like to switch gears one more time

and talk about the mortality estimate and challenges in estimating the mortality.

[Slide] There is a wide variability in the projected mortality for individuals in RESUS based on the proposed entry criteria. The risk of death is not equivalently distributed throughout the range of RTS scores. The proportion of trauma patients, as you have heard, who can potentially benefit from any life-saving treatment is a very small subset of the total trauma population. Most subjects, as you have heard, will survive their injuries and some subjects will die no matter what is attempted to help them. The RESUS trial does attempt to enroll the approximately 1 percent of the total trauma population that might benefit from an oxygen-carrying resuscitation fluid.

Finally, information on the proportion of serious trauma patients who are alive at the scene but die before reaching the ER is not easily available, nor is the information on the number of people who die prior to EMS arrival easily available.

[Slide] Because of the safety profile of HBOC-201, as you have heard, NMRC has attempted to enroll subjects at a higher risk of dying from hemorrhagic shock, with or without traumatic brain injury. The first proposal in the IND was to target a population with an overall

mortality rate of about 34 percent. However, the estimate was derived from in-hospital data and literature citations that represented retrospective analysis of data, with entry criteria that may not have matched the RESUS entry criteria sufficiently. Based on input from FDA, NMRC now proposes entry criteria of hypotension with RTS scores of 1 to less than 5. They also propose, as you have heard, to exclude subjects for whom blood is available quickly.

[Slide] The Revised Trauma Score is calculated based on three parameters, as shown in this slide. The weighted RTS score is derived from these three parameters by assigning a coded value to each of the parameters and then plugging the coded value into the equation seen in the middle of the slide. The RTS is heavily weighted by the Glasgow Coma Score, so small errors in coding the Glasgow Coma Score can result in large variations in the RTS. For example, a difference in Glasgow Coma Score between 8 and 9 can result in a difference in the RTS by the multiplier factor 0.93.

[Slide] The RTS cannot be computed unless there are data on all three components. The Glasgow Coma Score is heavily confounded by intubation, severe facial injury, intoxication, and drug use. There is no consensus in the literature for allocating verbal scores for intubated or pharmacologically paralyzed patients. Studies report a

loss of cases for analysis of between 3 and 28 percent, raising questions about the feasibility of determining RTS reliably in the field. As noted, difficulties encoding the Glasgow Coma Score portion can lead to large variations in the final RTS.

[Slide] This is the slide that was alluded to earlier by Commander Freilich. This was submitted to FDA in one of the IND amendments by NMRC. This figure does come from the Web site noted on the slide. This is a distribution of deaths solely as a function of RTS score. The data are derived from a very heterogeneous patient population, including those with only head trauma, those with hemorrhagic shock without head trauma, and so forth. It includes patients with blunt and patients with penetrating trauma.

Nevertheless, the information captured on the slide is illuminating. When evaluating death as a function of RTS, it becomes immediately apparent that the curve is sigmoidal in shape, with the steepest part of the curve in the middle. An RTS of 1 to less than 5 includes a population with a wide range of survival probabilities. In the middle of the range, with the entry criteria proposed by NRMC, one can see that small imbalances in RTS scores between cohorts can have a greater effect on mortality outcome than the 15 percent relative reduction in mortality

proposed as the primary endpoint of RESUS. Since RTS is weighted mostly by the Glasgow Coma Score, as we have seen, differences in coding for the Glasgow Coma Score can have a large impact on the RTS score.

[Slide] The number of subjects and the number of deaths are not equally distributed throughout the range of RTS scores, as we will see shortly and as you have seen earlier this morning in one of the presentations. The greatest potential benefit to offset risk is distributed predominantly to those with lower proposed scores, while the least potential benefit to offset risk is distributed to those with higher scores. Thus, for example, if the mortality rate were 100 percent, then even a small benefit would be seen to outweigh the risks. Conversely, if the mortality rate is only 10 percent, then the tolerance for adverse outcomes would be much less. We are here because we are somewhere in the middle.

Again, as already noted, small imbalances in the RTS score can have a greater impact on the outcome than the proposed therapeutic intervention and effect size.

[Slide] This slide is taken from information provided by the sponsor. You have seen it in a somewhat different format this morning. The National Trauma Data Bank captures in-hospital data, including hospital-arrival information. I believe that the data here cover four

years, from 2000 to 2004, and show again that there is a wide range in probability of survival based on entry RTS scores. Among these in-hospital subjects, only about 7 percent have concomitant blunt TBI. These in-hospital data indicate that those surviving to hospital arrival who are hypotensive in the emergency department and who have extremely low RTS scores have a very high probability of dying.

[Slide] Now we are showing you the data in a somewhat different format. This slide again shows that among subjects surviving to hospital admission, those with very low RTS scores due to extreme hemorrhagic shock are at very high risk of dying. Since RESUS proposes treatment in the field, it would be important to be able to identify this patient population in the field, as well as in the hospital. Whether it is possible to identify prospectively those hypotensive subjects in the field who are likely to remain hypotensive on hospital arrival would be a major challenge for the RESUS protocol.

[Slide] The next two slides look at the same type of information as we have just looked at, except that they consist of prehospital data from the same time period. As you can see from the first slide, the overall mortality rate is about the same as for the National Trauma Data Bank, but the distribution of subjects is different. Here

you see many subjects in the RTS decile 2.1 to 3.

[Slide] In the prehospital setting, subjects with traumatic brain injury represent about a third of the total population and subjects with traumatic brain injury are equally distributed in all of the RTS deciles here. The distribution of subjects and of mortality is different, as I have said, from the National Trauma Data Bank distribution, suggesting greater subject heterogeneity in terms of trauma. The higher mortality in the RTS decile 4 to less than 5 may be due to the inclusion of subjects with concomitant traumatic brain injury. The presence or absence of TBI does have an impact on survival probability. For subjects without TBI, the range of survival probabilities here was 7.1 to 62.1 percent, whereas among those with TBI, the survival probabilities ranged from about 19 percent to about 46 percent.

[Slide] Conclusions about the mortality estimate:

• Given the proposed range of RTS scores, the patient population is likely to be quite heterogeneous.

• While the ranges for mortality and the characteristics of the trauma victims differ in the three available databases, all indicate a very wide range of survival probabilities.

• While the overall average mortality is

approximately 58 percent, many subjects will have a probability of death that is much lower than the average.

I would like to switch gears one more time and talk about treatment effect.

[Slide] There is on clinical or preclinical basis to support the estimate of treatment effect for HBOC-201 in prehospital trauma resuscitation. It is not possible to estimate the potential magnitude of the treatment effect from clinical trials that have already conducted using HBOC-201 in surgery, and there have been no prospective, randomized, controlled Phase 2 studies performed or completed in consenting trauma subjects from which to estimate a treatment effect.

[Slide] The sponsor bases its estimate of treatment effect and its assessment of likely safety for RESUS on results of a subset of preclinical animal models of trauma and hemorrhagic shock.

[Slide] Limitations inherent to the animal models studied include their heterogeneity. We have already heard discussion about this. Many studies were not survival studies, while others clearly had survival as an endpoint. The type of hemorrhage varied. In some studies, hemorrhage was controlled, while in other studies it was not. There were also different resuscitation strategies, including fixed volume replacement, fixed blood pressure-

driven administration, and a combination of blood pressure with heart rate titration. Short and long transit times were modeled.

Other limitations of the models have already been discussed and include the use of anesthesia, warming blankets, and so forth.

[Slide] When the IND regulations were rewritten in the 1980s, the preamble to the proposed rule commented on the role of animal studies in clinical drug development. Preclinical tests are not intended to supplant data derived from adequate and well-controlled trials in humans, nor is safety information derived from animal studies intended to supplant safety data derived from clinical trials performed in humans. Thus, the results of preclinical studies do not establish a quantitative estimate of treatment effect and do not negate safety findings in completed clinical trials in humans.

[Slide] Proof of concept that HBOC-201 might sustain life in trauma has been shown in a variety of animal studies, in a variety of narrowly defined models of lethal hemorrhagic shock. Although animal studies should not be used to estimate a numerical effect size, nevertheless preclinical data could support studies of HBOC-201 in settings where an extremely high mortality rate is expected, such as massive hemorrhage, with or without

prolonged delay to definitive care, or in traumatic brain injury.

Now I would like to switch gears one more time.

[Slide] I would like to discuss three potential concerns we have over using HBOC-201 in the urban ambulance. They are risk of fluid under-resuscitation, difficulty in titrating the product, and the inability to manage treatment-emergent hypertension occurring en route to the hospital. The risk that treatment-emergent hypertension in a subject with uncontrolled bleeding could increase the risk of bleeding or re-bleeding is of concern in all trauma subjects, but especially in subjects with head trauma.

[Slide] RESUS dosing guidelines call for EMS personnel to target a conventional resuscitation blood pressure of 90 to 100 mmHg. This is based on the classic paradigm for fluid resuscitation using blood pressure as a surrogate for tissue perfusion. However, because HBOC-201 is vasoactive, targeting a conventional resuscitation blood pressure does not necessarily ensure adequate perfusion and could mislead EMS personnel into withholding additional crystalloid from patients who are actually hypovolemic.

NMRC has responded to this concern by amending the RESUS dosing guidelines. The guidelines now call for additional crystalloid to be infused in the face of a

systolic blood pressure greater than 100 mmHg if two or more classic signs of occult shock are present, such as thready pulse and cool extremities. However, not only do these signs have a low specificity for detecting hypovolemia, but it is not clear how to interpret these signs when using a vasoactive resuscitation fluid. Therefore, FDA is still concerned that this potential risk remains.

[Slide] NMRC contends that because RESUS subjects will be younger and have greater physiological reserve than elective-surgery subjects, they will be at lower risk of experiencing the excess adverse events observed in Biopure's elective-surgery studies. This table illustrates why this argument may not necessarily hold. Listed here are various aspects of medical care in elective-surgery patients experiencing uncontrolled bleeding and hypotension in the operating room, on the one hand, and field trauma patients experiencing these same events in the ambulance, on the other.

For example, patients undergoing elective surgery are medically optimized before their procedure. During elective surgery, numerous parameters of cardiovascular and respiratory function are closely monitored, many in real time. A wide variety of agents to closely control blood pressure are readily available. Use of fluid warmers

minimizes the incidence of hypothermia, a key trigger of impaired hemostasis in trauma patients. If necessary, additional personnel can be summoned for assistance at a moment's notice. Most important of all, there is a surgical team physically present in the room with the means to obtain rapid and definitive control of bleeding.

[Slide] Until relatively recently, the goal of trauma resuscitation was early and rapid normalization of blood pressure and blood volume. There is now considerable evidence that adherence to such a strategy prior to surgical control of bleeding exacerbates blood loss, reduces the concentration of clotting factors, as you have heard, and increases mortality.

Here are some excerpts from a review article reflecting current thinking on this topic, and I quote: "Although thrombus after an arterial injury is formed almost immediately, it is initially soft and jelly-like. Transformation to a more rigid hemostatic plug requires at least 20 to 30 minutes following injury."

Second, "Resuscitation strategies which cause abrupt increase in blood pressure and flow may increase hemorrhage volume.

[Slide] This table is from the current RESUS investigator brochure. It details the frequency of treatment-emergent hypertension in trials using HBOC-201.

The white boxes contain aggregate data from Biopure's BLA and the pink boxes contain data specifically from pivotal trial HEM-0115. Except for HEM-0115, data from trials in the white boxes are based on tables found in Biopure's final study reports. For HEM-0115, in the pink boxes, the tally is based on FDA's review of the actual AE pages contained in the case-report forms. We can see that for each population studied, the frequency of treatment-emergent hypertension was greater in the HBOC-201 arm than in the control arm. This applies not only to the aggregate population, but also for subjects under 70 years of age and those requiring medical management with antihypertensive agents. I call your attention to the information in the middle here, requiring intervention.

The olive-colored boxes contain data from Biopure's trial COR-0001, which you heard about this morning, a study recently conducted in Europe of 45 subjects undergoing elective percutaneous coronary intervention. Biopure has provided FDA with a copy of the manuscript and plans to submit it for publication in the very near future. Subjects in this trial were randomized to receive either .5 unit of HBOC-201, 1 unit of HBOC-201, or a low-molecular-weight starch solution, as part of the procedure, at an infusion rate of 7.7 mL/min. Treatment-emergent hypertension for this trial was defined as

systolic blood pressure greater than 180 mmHg.

As we can see, the frequency of treatment-emergent hypertension was nine versus zero for the pooled HBOC-201 cohort versus control arm, respectively. In one of the nine subjects, treatment with intracoronary nitroglycerine and intravenous nitroglycerine was ineffective in normalizing blood pressure, and the subject had to be admitted to an ICU for several days.

[Slide] The data on this slide come from the current RESUS investigator brochure as well. There were 45 orthopedic-surgery subjects in HEM-0115 who met the entry criterion of blood pressure less than 90 mmHg for infusion of clinical trial material and were randomized to receive either 60 grams of HBOC-201 or one unit of red blood cells, respectively. Please recall that a blood pressure less than 90 mmHg is also a RESUS enrollment criterion. Along the x-axis are post-infusion blood pressure responses, in deciles, for subjects experiencing a blood pressure greater than 130 mmHg. Total numbers are for 131 to 160 and then 131 to 140, 141 to 150, and 151 to 160. The y-axis indicates the percent of subjects in each category, and the boxes contain the number of subjects.

Although the sample size is small, we can see that there is a consistent pattern of higher blood pressure responses in subjects receiving HBOC-201 versus control,

with four HBOC-201 versus zero control subjects experiencing a systolic blood pressure of 151 to 160 mmHg.

The take-home message from this slide is that even though increased bleeding due to blood pressure elevations is problematic in the ambulance for any trauma subject with uncontrolled hemorrhage, it could be especially problematic in the one-third of RESUS subjects with closed head injury, because a rapidly expanding, space-occupying lesion cannot be addressed in the ambulance.

[Slide] In summary:

• HBOC-201 is a vasoactive product that is difficult to titrate and with a duration of action lasting hours, so if blood pressure overshoot occurs, prolonged countermeasures will be required.

• Even if blood pressure overshoot is detected immediately, stopping the infusion may not necessarily stop the blood pressure from continuing to rise.

• There is no safe and effective way to counteract blood pressure overshoot in the ambulance setting.

• Blood pressure overshoot can lead to clot disruption and increased bleeding or re-bleeding.

• Finally, in the ambulance setting, increased bleeding can be extremely problematic, particularly for

subjects with traumatic brain injury.

Now I would like to turn to a discussion of benefit and risk.

[Slide] In 1999, FDA, NIH, and DOD conducted a workshop on the safety and efficacy evaluation of oxygen therapeutics when used as red blood cell substitutes or as resuscitation fluids. In 2004, FDA issued draft guidance for the evaluation of oxygen therapeutics. This draft guidance suggested a hierarchical approach to the evaluation of safety that included an initial evaluation of products in a situation where adverse events were expected to be uncommon, thereby facilitating observation of safety signals. Such studies would be conducted in subjects who had been medically cleared, carefully monitored, and medically managed according to in-hospital standard-of-care guidelines, and the control would be red blood cells.

Demonstration of an adequate safety profile when compared with red blood cells allows an evaluation in less stable trauma subjects who are able to provide consent or unstable trauma subjects who are unable to provide consent.

[Slide] In the field setting, an oxygen therapeutic should have superior survival outcome when compared to an asanginous solution. It is entirely possible for an oxygen therapeutic to have an inferior safety profile when compared with red blood cells. Such a

product might even have clinical utility in reducing mortality in trauma in the field when compared with asanguinous solutions. But the problem is, designing such a study is very difficult, because it will not be easy to weigh the relative importance of safety signals and adverse events observed in comparisons against blood, against the potential benefit in terms of lives saved when the same product is compared against an asanginous solution, particularly if findings suggesting clinical benefit have not been observed in other settings.

[Slide] What are the challenges? There is wide variability in the projected mortality for individual subjects, which means that benefits to offset risks are not evenly distributed. We have already discussed that the magnitude of the effect size cannot be determined from animal studies, and the magnitude of the effect size is therefore uncertain. Prior human studies also do not provide a basis for estimating treatment effect.

[Slide] As I have showed you today, HBOC-201 was associated with increased adverse events of clinical importance in all analyses performed. These imbalances include an important imbalance in deaths as well. Many of the severe and serious adverse events I have discussed today can lead to death. Additional deaths due to medically serious adverse events will have the effect of

offsetting the potential benefit in terms of lives saved with HBOC-201. In addition, the net effect is to diminish the power of the study to detect a beneficial effect.

I would like to remind you that we are talking about additional deaths due to product-related serious adverse events.

[Slide] Victims of trauma, even young ones, may not have a lower risk for adverse events than older, medically cleared subjects undergoing elective surgical procedures. Put another way, excess adverse events noted in the HBOC-201 treatment arm in elective surgery could potentially be greater in critically ill trauma subjects.

Finally, transport times in the urban ambulance setting are short and the window of opportunity to benefit is small.

[Slide] FDA performed an extensive sensitivity analysis, varying assumptions for deaths due to SAEs, effect size, and the underlying mortality rate. We examined many different assumptions for mortality and varied effect size above and below the projection for RESUS. We also varied the percent of excess deaths due to product-related serious adverse events. After conducting this extensive sensitivity analysis, FDA found that the trial, as designed, is very sensitive to small fluctuations in the assumptions and is not robust.

[Slide] I would like to comment on risk-benefit analysis number 3 by the NMRC. The discussion this morning involved the benefit-risk analysis number 2, but I would like to talk about the benefit-risk analysis number 3.

The detailed methods and other information underlying this particular risk assessment in the issue summary have not been submitted to FDA, and therefore could not be reviewed adequately prior to this meeting. However, FDA does have preliminary concerns with the model, as presented. Documentation on validation of the model is lacking. Sensitivity analyses performed are incomplete and do not take the power of the study for each scenario described into account. The analysis using retrospective, *post hoc* subsetting of patient groups in HEM-0115 is problematic and may not be valid.

[Slide] I would like to comment on the restrictions on age. FDA's position is that the trial should not have an upper age limit. The fastest-growing segment of the trauma population is, in fact, the population older than 50, and more particularly, older than 70. Distinguishing subjects above or below a particular age under field conditions is likely to be difficult. Finally, older subjects may be at greater risk of ischemic consequences of severe hemorrhage, and therefore, paradoxically, might also potentially benefit more from

administration of an oxygen-carrying resuscitation solution.

[Slide] FDA has a number of concerns about RESUS, in summary:

• There is an excess of clinically significant adverse events in all analyses.

• Lack of preclinical and clinical dose-response studies to support proposed dosing.

• There is wide variability in projected mortality for individual subjects.

• The magnitude of the treatment effect cannot be derived from animal studies.

• The serious adverse events observed in previous trials, the uncertainty of the treatment effect, and the wide variability in expected mortality for individual subjects preclude a determination of a positive benefit-to-risk ratio.

• Monitoring and therapeutic interventions may not suffice to offset risks associated with the use of the product.

• Excluding the elderly may, in fact, not reduce risks associated with the use of the product.

[Slide] FDA asks the advisory committee to consider the following questions. You have seen them this morning, and I am going to repeat them here now.

[Slide] Question 1: Please discuss the following safety concerns raised by FDA, specifically:

• Safety signals and adverse events in previous clinical studies;

• The demonstrated vasoactivity of the product;

• The limited safety data for higher doses and rates of administration.

[Slide] Please discuss whether the available preclinical and clinical data are sufficient to estimate a treatment benefit for all-cause mortality at 28 days in the proposed RESUS trial.

[Slide] Question 3: After considering all of the available data, do the potential benefits outweigh the potential risks for individual subjects in the RESUS trial? (Please note that editorial change.)

[Slide] Question 4: Are there additional data that could help inform an assessment of benefit to risk in the RESUS trial?

[Slide] Question 5: Please comment on any modifications to the study design that might improve the benefit-to-risk ratio in the RESUS trial -- for example, a trial targeting a group with higher predicted mortality.

I would like to go back to question 3 and ask you also to consider the 21 CFR 312 standard of unreasonable risk when you consider this question.

Thank you.

DR. SIEGAL: Questions for Dr. Silverman?

DR. PICKERING: I have a question which relates to treatment-emergent hypertension. You placed a lot of emphasis on the coronary angioplasty study. It seems to me that that is an entirely different population from the one that we are considering. Do we know how many of those patients were hypertensive to begin with? How many of them were taking nitrates? Who knows what the interactions between HBOC and nitrates are?

DR. HESS: We have not yet received the final study report from that study, so I cannot answer those questions.

DR. PICKERING: The other question -- it isn't necessarily from there -- is, do we know what the time course of hypertension in the clinical studies was? Is it something that is seen within a few minutes of starting the infusion, or is it more delayed?

DR. HESS: I can't remember all the 353 patients that we reviewed. It was temporally associated with the product. I don't think there is too much doubt -- even the sponsor admits that there is a relationship between product administration and hypertension.

DR. PICKERING: But if it comes on within a few minutes and they are still in the ambulance, it's very

different than if it comes on after a couple hours or three hours.

DR. HESS: I think the former is more to my recollection, but I will defer until I have the data in my hand.

DR. FINNEGAN: It seems to me that the FDA has previously allowed some age restrictions. Can you give us the general FDA approach to age restrictions for products?

DR. EPSTEIN: The general concept is that we seek to have all relevant patient groups represented in a trial. We don't generally approach age restriction as a desirable exclusion. If there is a known basis for the exclusion, that can be another matter.

The same principle applies to many, many things -- gender and racial balance and so forth. We generally want all relevant groups included rather than having exclusions *a priori*. They don't all have to be present in sufficient numbers to be statistically analyzable as a subset, but that is also, in itself, desirable, when feasible.

DR. HINTZE: You have eliminated children and you have agreed not to take people less than 18 years. We heard this morning that we have eliminated soldiers on the battlefield, because it's difficult. I guess I don't understand why it's wrong to eliminate people over 70.

DR. SILVERMAN: If I had my druthers here, I would not leave out the pediatric population.

DR. HAUSER: Dr. Silverman, my understanding is that, unlike hypertensive strokes, traumatic brain injury bleeding is, in fact, not exacerbated by increases in blood pressure. Current evidence-based approaches to the treatment of intracranial hypertension include increasing the blood pressure specifically as a therapy for mass lesions within the head, even to the extent of giving alpha-agonists deliberately to increase the blood pressure.

Could you direct me to a resource, an evidentiary base, for the assumption that increasing pressure increases bleeding?

DR. LANDOW: Let me just tell you a little bit about my background. I was an anesthesiologist in a Level 1 trauma center for 20 years. I don't want to give you anecdotal evidence, but it would seem to me that it's self-evident that if you increase a source of bleeding in a closed space, the intracranial pressure will increase, unless it's treated. In fact, that's what patients do when they herniated. They actually can bleed into their heads, and if not treated immediately, they can die.

DR. HAUSER: I think that's absolutely incorrect and that prospective data demonstrate that that is not the case. There are lots of things in medicine which are self-

evident but aren't true.

DR. LANDOW: The only other source, I would say, is what we have received from SGEs. I don't want to reveal that person's name, but he is a world-famous authority. That's all I can say to you right now.

DR. HAUSER: I take care of 1,000 patients a year like that. I do it year in and year out, and I have for the last 25 years. I can tell you, it ain't true. And that is not what is in the literature. It's not just me.

DR. SIEGAL: Any other questions?

DR. EPSTEIN: I think we have to distinguish what FDA has put forward as a hold issue and what is not. Clearly, we have encouraged, in fact, the sponsor to include patients with traumatic brain injury, though not penetrating brain trauma, because we are aware that they are a significant constituent of the trauma cohort. We have not drawn a circle around it and said, "Because we are worried about vasoactive effects, we don't think they should be enrolled." Quite the converse; we think they should be enrolled.

We have also argued that there may be, based on some of the preclinical data, an advantage in giving an HBOC to patients with head trauma.

So I think we have, a little bit, posed the question wrong. FDA is not arguing against including TBI

patients who might get the vasoactive compound.

Similarly, I want to clarify the issue of age restriction. FDA has not argued that the NMRC's proposal to restrict the cohort to age less than 70 is a hold issue. It is not. We have simply argued that it would be desirable to include older subjects, because they will be difficult to stratify in the field. The patient is there in trauma. Is he 69 or is he 71? You just don't know.

We have also argued that the clinical relevance of including the older age cohort is important, because they are one of the most rapidly rising subgroups of patients where there has been trauma.

But again, the distinction here is that there is room for debate, and that is not a hold issue. What is most important, I think, for the committee to focus on are the issues that FDA has said are the cause of the clinical hold. I can reiterate those if they are not clear. They are the adverse-event profile that we believe we have seen in the human studies, the inability to extrapolate quantitatively from the animal trials to a conjecture of a treatment effect or a benefit in the RESUS trial, and our concern over the heterogeneity of the mortality risk for the enrolled subjects. We can explain a little bit more clearly, when we come to question 3, why that last point is material to a trial under waiver from informed consent. It

is because there has to be a reasonable conjecture of benefit to individual subjects, not just the group as a whole. So the heterogeneity becomes an issue of concern.

Again, what I am trying to do here is sort of keep the committee on track to focus on the hold issues, because, after all, the fundamental question here is, should FDA lift the hold? That's why we are debating the underlying science.

I hope that helps.

DR. SZYMANSKI: My question relates to the exclusion of the older individuals. Has it been shown that people with a prior vascular constriction, for instance, are more susceptible to adverse effects? That is why it would be reasonable to exclude people who are older and might have these problems.

The second question is, has it been taken into consideration in this study that HBOC-201 will be given only during a very short period of time, so that the adverse effects of vasoconstriction might be of shorter duration than in previous studies? Or does that make any sense?

DR. LANDOW: Let me tackle the second question. The product has a 19-hour half-life in the circulation. We saw from the graphs in animals that that hypertensive effect lasts at least two hours. I think the speaker said

that it returned towards baseline at three hours. So this isn't an effect that would be seen in the ambulance.

DR. SILVERMAN: With regard to the first question, this is a conjecture by the sponsor, that older people are at greater risk. Certainly the data show that there are more adverse events in older patients, but it is a conjecture as to why.

DR. KATZ: Dr. Silverman, we heard from one of our colleagues on the committee, with substantial experience, something that has been my clinical experience as well, and that is that -- I will conjecture a little bit -- the people who will be enrolled in this trial are maximally vasoconstricted at the time that care is delivered, as a result of severe hemorrhage and hypotension. Most of the adverse-event data are in people that were hemodynamically stable, by virtue of their selection for elective surgery, at the time that they were enrolled. What is your response to that?

DR. SILVERMAN: You saw information on a number of people who were hypotensive as their reason for infusion of the product, and you saw the result of administration of a single two-unit -- 60 grams of the product. Nine of the 25, or 36 percent, had blood pressure elevations greater than the target of 130 and four of them were above 150.

DR. KATZ: We didn't see details of what other

resuscitation was going on at the time that that occurred, however.

DR. SILVERMAN: That's true.

DR. KATZ: I'm presuming they were also getting fluid boluses, and perhaps even pressors, at the same time.

DR. CRYER: May I also ask, in those patients, was the response immediate? They were obviously anesthetized if it was, because they were in the middle of an operation. It really seems like it's a different group of patients than we are talking about here.

DR. LANDOW: Yes, I agree. But still keep in mind that anesthetics reduce sympathetic outflow. In a subject who was not anesthetized, you might have even a more exaggerated response -- the person in the ambulance, for instance. We just don't know. We just don't have the data to answer most of your questions. That's one of the problems.

DR. CRYER: Well, it sounds like we need some.

DR. LANDOW: We agree.

DR. FLEMING: I guess I may be asking a similar question. The issues that were put forward relative to the clinical hold -- certainly I understand the issues about how we are having great difficulty in understanding how to extrapolate the animal data to establishing efficacy expectations, or even safety expectations. I also

understand from the available 1,400 patients that have, in fact, been involved in randomized trials in the 0115 study, as well as the totality of data, that there are certainly very significant safety issues that have been identified. What I am struggling with is how reliably we can extrapolate those safety issues to the context of the RESUS trial. I have heard statements now that have gone in both directions.

While there are these substantial safety risks that have been seen in 115 and, more broadly, in the Phase 1-2-3 data that are available, is it likely that in the context of RESUS, those issues will be worse, the same, or less?

DR. SILVERMAN: That is, I think, the $64 million question. We don't know.

DR. CRYER: Part of the hold has to do with the adverse events. I would encourage you to think about the adverse events that occur now from the use of Ringer's lactate solution, the resuscitative fluid in ambulances. If you took this patient population and you counted up the adverse events they had and you blamed it all on Ringer's lactate in the ambulance, it's astronomical. Every one of these patients is going to have three or four adverse events, 10 times more serious than any of the ones that I saw on those charts.

Do we have any idea of what the adverse-event profile might be expected to be in the control group?

DR. LANDOW: Let me just clarify what I said a few minutes ago, that we wanted more data. What I meant to say is that we want more Phase 2 data in-hospital, in the ER, in consenting trauma patients, hopefully. But with these questions that we are asking, that doesn't mean that the way to get that information is from a Phase 3 trial without informed consent. That's what I should have said. We need more Phase 2 data in subjects who are consenting to this. That way, then we can set the foundation for lifting the hold.

DR. KATZ: Let me try something rhetorical. If the group was homogeneous with a 58 percent mortality, would you feel the same way?

DR. SILVERMAN: I think it's very important to make the point that these were controlled studies. These were excess adverse events that we were talking about here. These were controlled studies, all of them.

DR. FLEMING: That is an important clarification. We do have 1,400 patients, and the data that we are looking at -- in particular, the data that I want to come back to later on is in the FDA briefing document, on Table 3-B, on page 51 -- are talking about excess events in a controlled setting. So you make a valid point. You have disease-

related events and you have intervention-related events. But the signal that is being put forward here is a signal from excess events in a randomized, controlled setting.

When we get back to a more detailed discussion, I am persuaded that there is a very significant issue here in the context of the studies that have been done. The question that I am struggling with is, to what extent does that excess likely translate to the context of the RESUS study?

DR. SILVERMAN: If you go back and take a look at the slides that I had here, the draft guidance document spells out an approach. You kind of back into these clinical trials. If you have a randomized clinical trial against red blood cells and have an adequate safety profile in that context, then you have a basis for moving forward in this other setting. When you don’t have an adequate safety profile, which I believe we do not have here, then you wind up in the situation that we are all in here today, discussing how to get there.

DR. HAUSER: I am struggling here with the concept of hypertension as an adverse event. As a surgeon and as a person who takes care of trauma patients and as a person who trains residents, I specifically train my residents to ignore hypertension, that it’s hypotension that is our enemy in trauma, and not hypertension, and to

leave it alone, unless it gets way, way, way out of control. There is more damage done by trying to control hypertension in trauma than by trying to prevent it.

So I really see this as a question of how you see the elephant. For people who come from a background, perhaps, of internal medicine, where hypertension is a disease, or who come from a background of medical neurology, where hypertension leads to stroke and to renal failure, this is an issue. From the point of view of someone who takes care of hypotension all the time, I think hypertension is a blessing. I like to have it more frequently in my patients because I consider it a buffer. It means that if they are going to continue to bleed, which they are -- now, perhaps they are going to fall off the edge, because they are really vasoconstricted, a little faster, but that's a buffer against my main enemy, which is hypotension, and I would like to see it more often.

DR. ALAYASH: May I just comment on that? I pretty much agree with what Dr. Hauser is saying about hypertension being not necessarily a major adverse event. But I would like to point out that hypertension indicates that we are dealing with a vasoactive substance and that we are getting vasoconstriction. So when you are looking at trauma patients -- some of them may be in their 30s, some of them may be in their 50s and older -- many of them have

underlying coronary-artery disease. I would submit that a vasoactive substance with vasoconstriction does pose problems and that there is a possibility here that the hypertension is really a measure of the degree of vasoactivity of the product.

DR. HAUSER: I would like to accept that vasoactivity as a therapeutic event in many of my patients. It avoids the necessity of giving some of them epinephrine or phenylephrine, which we end up doing under certain circumstances.

DR. KLEIN: I would like to just push that point a little further, because maybe some of the physiologists and the people who do anesthesia and are smarter than we internists can help clarify this. To me, the hypertension is just a signal. What bothers me a lot is that virtually all of the HBOCs used in the past have had excess myocardial infarction, cardiac lesions in animals, or strokes associated with their use. There are certainly a lot of data to suggest that this, in part, is an issue of microvascular circulation. Whether that is due to NO scavenging or facilitated oxygen delivery, I don’t know.

I am concerned that, with these compounds, when you give them in the course of treating someone with trauma or anything else, you are not really sure what it’s doing in the microcirculation. We do know that with trauma you

tend to shift perfusion away from the surface internally. I am concerned that perhaps the mechanism of adverse action of some of these compounds is to do something to the microvasculature, where you have just shifted, resulting in strokes, myocardial infarctions. Again, I am concerned that it isn't just the elevation of blood pressure, pulmonary artery pressure, systolic blood pressure, but that that is just a signal of something going on elsewhere.

DR. HAUSER: I think those are very good points. That is one of the things that the animal data addressed. As you say, there is not, in fact, excess myocardial pathophysiology on microscopy in the animals. In fact, there appears to be a shift, if anything, of blood flow away, perhaps, a little, from the liver -- we look at oxygenation in the liver instead of pressure; we are looking at oxygenation as an end product of blood flow -- away, perhaps, from the liver and towards the brain, as measured by fluorescence oxygen electrodes. Those are insensitive to pressure and sensitive to oxygenation.

So I think are pushing, apparently, the blood flow in the right direction for these patients, which is towards the brain. At least the myocardium appears to be neutral. In terms of the blood flow in the gut, I think that we are seeing some diminution. You are absolutely right. There are those who would say that that's going to

lead to excess organ failure postoperatively, via the mechanisms that Deitch and others have talked about with ischemia reperfusion of the gut.

But as I said before, I will take those patients in the ICU as organ-failure patients any day, if they are alive.

DR. SIEGAL: If I may, we have really gotten into our open discussion, but it is time that we had the open public hearing part of this meeting, so that we can then proceed to our own deliberations.

With that, I am going to turn this over to Don Jehn, who has a couple of statements to read.

Agenda Item: Open Public Hearing

MR. JEHN: FDA received a couple of statements prior to the meeting from SGEs who initially reviewed the clinical proposal of Navy and then did the review, the updated one. One was a temporary voting member for the meeting, but he became ill and is not here, Dr. Demetriades.

This is his statement:

“I have reviewed all the documents and new material related to the product. In my opinion, the FDA should not approve this study, for many reasons. The clinical studies for orthopedic patients showed increased complications related to systemic and pulmonary

vasoconstriction. In hypotensive patients, there is already a significant vasoconstriction, and administration of the product may make things even worse. In addition, we have good experimental and clinical evidence that aggressive resuscitation in hypotensive patients increases bleeding and mortality.

"The current teaching suggest that in an urban environment the paramedics should 'scoop and run.' There is a possibility that the study group will show a higher mortality than the controls. If this happens, in view of the extensive publicity of the study in the mass media, it will be catastrophic for the FDA, the military, and the trauma community. From the academic trauma point of view, I am concerned that it will be a setback to any future efforts to perform studies with waived consent.

"Some other thoughts:

"Mixing blunt and penetrating trauma together is not appropriate. It is very rarely that blunt trauma patients die within the first one hour because of massive hemorrhage. The bleeding in blunt trauma is usually the result of solid organ injuries -- i.e., liver, spleen, kidney -- or fractures. It is highly unlikely that this kind of injury will result in hemorrhagic death within the first one hour.

"For the purpose of this meeting, I did a

preliminary analysis of my trauma registry. In patients with field blood pressure less than 90 and excluding those with severe head trauma (head AIS greater than or equal to 3), the overall mortality was 20 percent, 84 of 422 cases, in blunt trauma and 33 percent, 96 of 298 cases, in penetrating trauma. It is obvious that you cannot mix these patients. I think it would be more acceptable if the study population includes only penetrating trauma patients with a field systolic pressure less than 80 mmHg. It is likely that in this group of patients the benefit may outweigh the risk."

Then there is a shorter statement from an SGE who did a review of the initial and also the final:

"I have gone over the changes in the resuscitation protocol for the December 14th BPAC meeting. I think the change in resuscitation blood pressure is appropriate and could even be lower, since any rise in systolic blood pressure may aggravate re-bleeding. I do not have any comments on any of the other changes.

"My major reservation about the product still remains, based on the human data. I do not believe that the animal studies can refute the high risk of cardiac, renal, and other causes of mortality."

That's all. I will turn it back to the chair. He is going to read a statement prior to the open public

hearing.

DR. SIEGAL: I am obligated to read this verbatim, announcement for particular-matters meeting -- e.g., product-specific.

Both the Food and Drug Administration (FDA) and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

MR. JEHN: We have 13 requests to speak during

the open public hearing. Go ahead.

DR. SIEGAL: All right. The first is Sidney Wolfe. Each of you has four minutes.

Agenda Item: Sidney Wolfe

DR. WOLFE: I will tell you that I do not have any financial conflict of interest.

This presentation is based on the data made available yesterday morning by the FDA on the Internet. Although you have heard some mention of the number-one reason for the clinical hold -- namely, the large increase in adverse events in the controlled trials in the people getting HBOC-201 -- I just want to spend a little bit of time with that.

[Slide] First, just the reasons for opposition to lifting the clinical hold: Previous clinical data demonstrate large increases in risk. Animal models are much less relevant, for a number of reasons that you have heard, and therefore do not trump previous clinical data from controlled trials. Again, this is not anecdotal clinical data. Study design is not relevant to either people in rural areas or in military settings, in both of which prehospital intervals are much longer.

The absence of informed consent, in light of the above, would be unconscionable, but even with informed consent, this trial cannot seriously be said to be

equipoise. Equipoise, as you know, is the ethical concept where you don't have any less or more likelihood of benefiting from one or the other. The data on the serious adverse events just belie that enormously.

[Slide] These were the data in people under 70. A lot of focus was made on the fact that if you excluded people who were older, then you wouldn't have any problems. Just to point out, for death, there were nine in the HBOC-201, three in the control group, and so forth. Total serious adverse events -- and these are not just hypertension, which is worrisome enough, but these are actual clinical events (death, dialysis, acute renal failure) -- 76 in the HBOC-201 group and 26 in the other.

[Slide] This is again from FDA data. These are the people who had controls that were not consisting of blood. Again, the total number of serious adverse events is 40, versus 15 or so -- a large, large excess. Even though, at an individual level, it's not statistically significant, if you make composite endpoints, which are done, there is a large excess.

[Slide] This is reviewer number 3. This is one of the more poignant statements, which I think covers a lot of what the discussion has been so far. In the real world of trauma care, the fraction of patients that will benefit from such treatment is probably small, a few percent at

best. However, the presence of injury and hypovolemia will raise the fraction of patients having bad reactions to HBOC by creating unusual patterns of altered perfusion, bacteremia, endotoxemia, and inflammation.

[Slide] Thus, the animal model probably overestimates benefit and previous clinical experience almost certainly underestimates the toxicity of these products. The end result is that the net benefit for giving an HBOC is likely to be less than the toxicity observed in the earlier human trials and the benefit far less than the toxicity when given to trauma patients.

[Slide] This is just on the issue of heterogeneity and the FDA's discussion of heterogeneity and the expected mortality of individual subjects -- again, individual subjects because when you waive informed consent, it has to benefit that person, not just, statistically, the whole group. The major concern was, according to the FDA, that many subjects who ordinarily would survive and do well without HBOC-201 will be exposed to its risks. This is a central concern for a trial performed with waiver from informed consent.

[Slide] This is reviewer number 6 (I would identify these people, but I don't know who they are): It would appear that HBOC-201 has significant risk for hypertension and, in a sense, acts as a vasopressor because

of its binding with nitric oxide. The real question is whether the oxygen-carrying capacity of the Hgb solution is of enough benefit to offset the risk of hypertension, myocardial infarction, cerebrovascular accidents, and renal complications. Based on previous analysis by the FDA and Table 5 (in what this person reviewed), the benefit-to-risk has not been achieved.

In summary, I would say that, aside from what you are reading up there, I don't think anyone disputes that there is a need for something to take the place of the blood that can be given once you reach the hospital emergency room. This product is far too dangerous. I think as much research as possible needs to be done to develop a product that actually meets this need without these enormous risks that have been documented in humans.

Just to summarize, human subjects would be exposed to unreasonable and significant risks. Participation does not hold out the prospect of a direct benefit for an individual patient. The previously stated FDA reasons for disallowing the study to begin are still quite valid.

Thank you.

DR. SIEGAL: Thank you, Dr. Wolfe.

The next speaker is Adil Shamoo.

Agenda Item: Adil Shamoo

DR. SHAMOO: Thank you very much for allowing me to address this advisory committee.

I am Adil Shamoo. I am the bioethicist for the RESUS study. I am also a former chairman of biochemistry, so I have dealt for over a quarter of a century with real data.

[Slide] Whatever I say is really a small portion of a letter to the editor published last June in a special issue of *American Journal of Bioethics*. So my private advice to the NMRC is public, basically, and I stand by both of them.

[Slide] I have a conflict of interest. I have been a paid bioethics consultant to the NMRC, as well as being a member of their advisory board. But I have not been paid by any other industry related to this, including Biopure.

[Slide] Let me tell you what I said -- I don't know if the people at FDA remember this -- in 1995, when FDA was about to issue the informed consent rule. I said a lot of bad things about it, as a matter of fact, and I still think this is a very troubling type of experiment. I am one of those -- maybe there are one or two here who know my publications and my statements to the public or testimony before Congress -- I all the time came down to the protection of human subjects. There have to be

compelling and unique reasons to put human subjects, especially without their consent, into an experiment.

I said, “In 10 years, we will have had some abuses, and people will start rethinking the rules.” That is exactly what FDA -- I commend them; they are actually reviewing the rules. Hopefully, they will put more restrictions on them.

[Slide] This is very ethically challenging research. Therefore, there must be compelling reasons to do that. The compelling reason is 58 percent mortality. That’s a very high death rate. As a society and as individual members of that society who may use those services, it forces us to think it through. At the same time, just because we need that kind of progress in science, that doesn’t mean we just simply comply with the regulation. We have to go beyond compliance with the regulation. We have to bend backward and protect human subjects.

[Slide] In my thinking for years, the protocol must go beyond just compliance.

I don’t want to badmouth anybody else, but our protocol is way better than one approved by the FDA. For example, we have a flash card for members of the family or the subjects themselves for informed consent. We have an abbreviated version of informed consent, in case somebody

can read it within the therapeutic window. The minute we arrive at the emergency room, we use the standard of care, et cetera.

We must have well-trained and educated staff. In my experience with the staff for three years, they are very well-trained and they are very sensitive to ethical issues.

We must have strong and continued oversight. The Data Safety Monitoring Board has an absolute standard of stoppage.

We must have transparency. Last June, in my paper, I recommended, contrary to what the current practice at NMRC was, that all data, all correspondence, everything related, should be made public. This BPAC meeting, with all the documents, is now available to the public.

But I will even go further. Everything else should be made open to the public. But this goes far into satisfying that.

We must pay unique attention. I can’t go through this with you in the few minutes I have. We must pay attention to risks and benefits and the calculation and fair subject selection.

Basically, I have sat down with them for three years. I have read all the data, all the correspondence. It is my judgment that this experiment should move forward and the hold should be lifted.

Thank you very much for listening to me.

DR. SIEGAL: Thank you, Dr. Shamoo.

Debra Daniels.

Agenda Item: Debra Daniels

MS. DANIELS: My name is Debra Daniels [phonetic], and I am a recipient of the Hemopure product in the South Africa trial.

Biopure did cover my travel expenses for me to be here, but it doesn't have an effect on what I am about to say.

In July 2005, while traveling in South Africa with my college, I fell victim to a violent crime and had to be admitted to the Johannesburg General Hospital Trauma Unit. After waiting over an hour for the ambulance to arrive, I was admitted to the emergency room, with a stab wound to my chest, a punctured lung, and a substantial amount of blood loss. When I arrived at the hospital, I was asked if I would like to participate in the Hemopure study. Seeing as I was in a state of shock, I said that I did not know. The hospital then contacted my father here in the U.S., who gave his consent for me to participate in the clinical trial of Hemopure. Due to the large amount of blood loss and the severity of the stab wound, my blood levels were critically volume-depleted. I received Hemopure, which successfully worked as an oxygenating

bridge.

The product worked well as initial frontline therapy. I subsequently required only two units of packed red cells, thereby limiting my exposure to human blood products.

In light of such a dramatic and successful outcome regarding my personal experience, I would sincerely hope that Hemopure would be made available to everyone in life-and-death situations, such as our armed forces overseas.

Hemopure worked as a blood substitute in my situation and delayed my need for packed cells. I think in emergency situations where human blood products are not available or are in short supply, Hemopure would make a fantastic substitute and could help save many lives.

To the very best of my knowledge, Hemopure was an intricate part of the process that took place in the emergency room in Johannesburg which ultimately saved my life.

Thank you.

DR. SIEGAL: Thank you, Ms. Daniels.

Is Dr. Boekenberg [phonetic]?

Agenda Item: Dr. Blackenberg

DR. BLACKENBERG: Mr. Chairman, I would like to thank the committee for the opportunity of addressing this

meeting today.

My spouse is a paid consultant to the Biopure Corporation. However, I have no financial interest or connection to the sponsor or Biopure Corporation. I have not received any financial assistance to travel to this meeting.

As you can hear, Mr. Chairman, I'm South African. Where I come from in South Africa, Hemopure is a fully registered product. It's available for routine use.

I am a specialist anesthesiologist in private practice in the Johannesburg area in South Africa.

Since the regulatory approval of Hemopure in South Africa, I have participated in the physician training program offered by the manufacturing company and have subsequently had the opportunity to administer this product in routine clinical practice to more than 30 individual adult surgical patients. I have used Hemopure in this context both as a red cell alternative in the management of acute surgical anemia and as a volume expander for the treatment of patients suffering from acute surgical hypovolemia.

I would like to place on record that in each of these patients, the administration of Hemopure has resulted in improved physiological and clinical parameters, indicating adequate oxygenation. On no occasion have I

encountered a product-related serious adverse event that has necessitated the discontinuation of Hemopure administration. In cases of acute surgical anemia where red cells have not been an option for treatment, this product has proved to be an adequate alternative to blood transfusion.

On the basis of my limited but satisfactory experience with Hemopure in routine clinical practice, I have no reason to believe that utilizing this product in the RESUS trial protocol will place patients at substantially increased risk of suffering a serious adverse event, particularly if the administering personnel are appropriately trained in the use of Hemopure. I would therefore strongly support proceeding with a carefully controlled, prospective, randomized clinical trial in major trauma patients.

Thank you.

DR. SIEGAL: Thank you, Dr. Boekenberg.

Agenda Item: Lewis Levien

Dr. Lewis Levien.

DR. LEVIEN: Mr. Chairman, ladies and gentlemen, thank you for the opportunity of addressing this meeting on this important topic.

[Slide] I am a paid consultant to the Biopure Corporation, and it is in this capacity that, as part of

our regulatory approval process, we were instructed to collect the data very carefully in a prospective manner in the first 80 consecutive cases who received this product as a registered product in the South African environment. This formed the basis of carefully collected data, with a clinical research assistant at the bedside collecting the data during the administration.

Subsequently, in an ongoing process, an additional 277 patients have received this product in general application. This is ongoing.

[Slide] This forms the basis of a publication which has been circulated to the committee members. I will not dwell on any of the components, because the information is available. But I would like to draw to your attention that the mean usage in the first 80 patients is very similar to that which is going to be used in the RESUS trial and the plasma hemoglobins achieved are very similar.

[Slide] The SAE rates which were observed in the initial 80 patients are remarkably similar to the SAE rates in the optimum group, the 115 subset, and less so than the complete database. The majority of these SAEs were related to the underlying disease process.

[Slide] Except these which are listed here. The sudden death was not thought to be product-related, but, because of its serious nature, was included.

So we can see that the SAE rate is relatively low in this group of patients, where it was possibly or definitely product-related.

[Slide] The balance I am not going to dwell on. It's in the publication. It mainly is the typical mix of surgical patients.

[Slide] Why did we see this improved safety profile? We believe it's because all the physicians who participated in the first 80 patients attended the structured training course, learned from lessons learned in the clinical trials. We advised avoidance of the over-age-70 age group on the basis of the safety profile. These risk-mitigation strategies are really contained in the RESUS protocol.

[Slide] Much has been said about the vasoactivity of this product. Here are the blood pressure recordings during the screening period and after each infusion, before and during each infusion, taken for the first 80 patients on a minute-to-minute basis. You can see that with relatively small risk-mitigation strategies, such as varying the rate of dosage and actively treating those odd patients who did manifest with increased blood pressure, the blood pressure recordings remained constant and flat throughout that group. So it wasn't a clinical problem.

[Slide] The subsequent 277 patients -- again, the same sort of usage as with RESUS.

[Slide] Fluid overload remaining the one serious aspect that required attention.

[Slide] Specifically, Mr. Chairman, in the group of greater than 350, there were no cases of stroke or TIA, no clinically significant methemoglobinemia, no acute myocardial infarction, and no hepatic dysfunction, although we commonly saw the typical pigmentation of the bilirubin breakdown products.

[Slide] In conclusion, Mr. Chairman, many of the patients in whom this product was successfully used either had profound surgical anemia or severe hypovolemia in elective surgery on occasions gone wrong, and included a subset of patients who were resuscitated with this fluid, as with the RESUS study.

[Slide] The data collected from clinical use of Hemopure in South Africa is very similar to that observed in the less-than-70 age group in the 115 clinical trial. On the basis of the favorable safety information, these data support strongly proceeding to a well-constructed, prospective, randomized clinical trial in major trauma, as described in the RESUS protocol.

I thank you for your attention.

DR. SIEGAL: Thank you, Dr. Levien.

Kenneth Kipnis?

DR. ALAYASH: May I just make a quick comment? The FDA would appreciate getting all of these data in their fullest detail. I think these are important data. Coming from South Africa myself, I know that, for example, certain populations, like the black population, have different incidences of myocardial infarction. So there could be an influence of the ethnicity, the gender, and the population involved.

Agenda Item: Kenneth Kipnis

DR. KIPNIS: I'm Kenneth Kipnis from the University of Hawaii. I'm in the Philosophy Department. I write extensively on research ethics.

I want to acknowledge the Navy's underwriting my appearance here and acknowledge that I was asked to serve on a data safety monitoring board for what was then called the Hemopure trial.

A bit about adverse events. Adverse events are a feature of many medical treatments, both standard and investigational. Of course, it would be better if patients could be screened for susceptibility before placing them at risk, but if the tests aren't there, optimal care will require decision making under conditions of uncertainty. One then needs confidence that the risks of administering an imperfect but effective treatment are smaller than the

risks of the untreated underlying condition. Blood transfusions, for example, will kill some patients even if they are impeccably administered. But like any imperfect treatment, transfusions should still be used if withholding them significant increases the risk of death.

In considering adverse events, much depends on the gravity of the underlying condition. As Christiaan Barnard, the South African heart surgeon, has observed, it makes sense to leap into a crocodile-infested river to escape from a lion, but not if there is no lion. Metaphorically, the subjects in the proposed RESUS trial are pursued by lions. They are in severe hemorrhagic shock secondary to trauma. Their tissues are becoming oxygen-starved. Even with excellent care, there is a better-than-even chance that they will die, very likely before reaching a hospital. It is a problem that blood transfusion, the standard of care, is not available in the field. Apart from slowing blood loss, replacing fluids, and speeding the patient to a hospital, EMTs have nothing for hemorrhagic shock. It would be a major medical advance if this could be remedied.

While commendable, the scrupulous attention to AEs and SAEs misses some aspects of the bigger picture. Remember that roughly three out of five of these subjects will not survive.

What we need to be looking at, by the way, is FAEs, fatal adverse events.

In the context of this trial, there are two gaps in our understanding. First, no one now knows whether -- and if so, how far -- HBOC-201 can reduce mortality. Evidence at hand suggests significant efficacy. I have heard 15 percent to 75 percent today. Who knows?

Second, despite the efforts to reduce risk, no one now knows whether the adverse effects of HBOC-201 will cause the deaths of subjects, and if so, how many. Evidence at hand suggests that some deaths are expected. We have heard 1 to 2 percent today.

The RESUS study will illuminate both the efficacy of HBOC-201 in reducing mortality and the risks as a treatment for severe HS. Scientifically, this is the reason this research should go forward.

Clinically, the same evidence also suggests that the number of lives that will be saved using HBOC-201 will be significantly greater than the number of lives that will be lost as a result of adverse events. Given that EMTs have nothing that can restore oxygenation, the use of HBOC-201 for this purpose makes clinical sense. Though no one now knows, it is not unreasonable to expect that subjects in the experimental arm of the study will have a lower mortality rate, even with adverse events, than the subjects

in the control arm. A data-monitoring committee will ensure that this expectation remains well-founded.

Given, as here, that the medical condition is seriously life-threatening, that EMTs have nothing that can restore the oxygenation of tissue, and that the use of HBOC-201 is a responsible attempt to provide care that is significantly better than the standard treatment -- notwithstanding a possibly imperfect safety profile -- the RESUS study would appear to measure up to both the scientific and clinical standards for such research. For these reasons, I submit that doubts about the safety profile of HBOC-201 should not be a bar to the approval of this study.

Thank you.

DR. SIEGAL: Thank you, Dr. Kipnis.

Dr. Aryeh Shander.

Agenda Item: Aryeh Shander

DR. SHANDER: Mr. Chairman, committee members, thank you for giving me this opportunity.

[Slide] Before I start, my disclosures: I have been a consultant to Hemosol, to Alliance Pharmaceutical, and now to Biopure. My travel here is underwritten by a grant from the Henry Jackson Foundation, associated with NMRC.

I would like to offer maybe the only definitive

statement made today: It is cooler in the room now. [Laughter]

[Slide] As you can see, my name is Aryeh Shander. I am the clinical professor of anesthesiology and trauma medicine and surgery, Mt. Sinai School of Medicine, New York. I am also chief, Department of Anesthesiology, Critical Care, Hyperbaric Medicine at Englewood Hospital and Medical Center in New Jersey -- if you are wondering, Exit 21.

I am a clinician who practices with a large number of patients for whom blood is not an option. I come to you with a concern that the current strategies to improve morbidity and mortality are very limited, and the introduction of an artificial oxygen carrier -- long-awaited, I must say -- would without question save lives, with what my colleagues and I consider an acceptable risk.

[Slide] My reason for being here is to describe to you the rather unique origin of RESUS. As a result of the tumultuous time after September 11, 2001, a group of committed and concerned physicians, many of whom are here today, met in Philadelphia to reevaluate the process of initial resuscitation with the available fluids and modalities in 2001. This group was known as STORMACT, Strategies to Reduce Military and Civilian Transfusion. STORMACT asked the four fundamental questions that were put

before the group:

• What to do until blood is available?

• What if blood becomes available, but is not enough?

• What to do to conserve the limited available blood?

• Lastly, how to best manage the available blood until a definitive destination is reached?

[Slide] These are all familiar questions, and, again, situations encountered both in the military and in the civilian environment, and to some extent in the operating room arena. In the documents submitted to this committee, STORMACT addressed all modalities of resuscitation and amended them according to the new available information, both at 2001 and thereafter.

Of interest, the U.S. Special Forces adopted some of these recommendations rapidly, and many are currently becoming part of the armamentarium for civilian prehospital resuscitation and blood conservation for the hospitalized population.

[Slide] RESUS, one component of STORMACT research recommendations, addressed artificial oxygen carriers generically. It was only after the establishment of the advisory committee by the Society for the Advancement of Blood Management and the Naval Medical

Research Center that selection of HBOC-201 occurred.

Again, I would leave you with a thought: RESUS is the child of September 11, 2001, born under devastating circumstances, independent from industry. It has had a painful and tortuous growth, with very slow development. The principles of its genesis are still plaguing the medical community, both abroad and at home.

Blood, a precious commodity, can improve survival, but is limited to specific situations. For us, the clinicians, it is an answer to many of these situations, but is unavailable in some situations where life is dangerously at risk. We must be allowed to explore this agent in order to help our patients.

I thank you.

DR. SIEGAL: Thank you, Dr. Shander.

Sergeant James Wright and then Colonel Wright.

Agenda Item: Sergeant James Wright

SERGEANT WRIGHT: My name is Sergeant Wright, United States Marine Corps. I have to say that the Navy has paid for my trip out here.

But that has not been the motivating factor in my opinion. My opinion towards this product, as a layperson, is based on my experiences in combat, my injuries, and the injuries of the Marines that I serve with, some of whom didn’t make it off the battlefield.

A little background -- I don't have any slides, no graphs, sorry about that -- how I came to be missing my hands. April 7, 2004, we were on a patrol on the south side of Fallujah, ambushed by about 40 to 60 Iraqi insurgents. During the course of the ambush, I was struck by a rocket-propelled grenade, which immediately severed both my hands and severely damaged my left leg. I had an open fracture in my femur and some arterial bleeding.

We didn't have the luxury of a hospital out there. It took 45 minutes for the MEDEVAC chopper to come and take me off that battlefield. We used bungee cords for tourniquets, one of which I still have as a souvenir.

One thing that comforted me out there on the battlefield, in spite of my injuries, was knowing that I had some very capable friends and Navy corpsmen out there to take care of me. As I told somebody earlier today, if you would have told me that there was something out there that you could administer to me, with a slight risk to my health -- I would pour tar in my veins. It didn't matter what it was; if you told me it would help me, I would be very willing to allow that as a risk, especially when I have other risks at the same time, such as lead flying down, hitting the ground, the vehicles, and the Marines around me.

I am not a recipient of the Biopure product, but

as a combat-wounded veteran, I think that in certain situations any risks that I have been hearing about today are not applicable to our situation. In my view, there is no gray area. There is no, “Well, you know, this might make this Marine sick.” It’s, “Either he is going to die or we can try this.” I’m willing to bet that 100 percent of the victims out there in the battlefield are willing to try it. I’m willing to bet that my platoon commander, Captain Brent Morel, whose Navy Cross probably consoles his wife little, since he didn’t make it off that battlefield -- he bled to death out there -- if there was a product like this that may have brought him home, it would be well worth the risk in applying it.

That’s all I have for you. Thank you very much for your time. Thank you for allowing me to speak my opinion.

[Applause]

DR. SIEGAL: Thank you, Sergeant Wright. Now Colonel Wright.

Agenda Item: Colonel James Wright

COLONEL WRIGHT: Ladies and gentlemen, members of the committee, FDA: I am James Wright. I’m the surgeon for the 720th Special Operations Group, Air Force Special Operations Command, and if you haven’t guessed it, Eddie Wright’s father.

I have no conflict of interest, other than that the Navy paid for my travel here today.

I would like to tell the committee a few things about Sergeant Wright and make a few remarks about the need for HBOCs in Special Operations Forces.

When Eddie was wounded and lying on the floor of that Humvee, going into hemorrhagic shock, feeling himself getting lightheaded, he realized that to get out of that battlefield, he was going to have to take charge. And he did that. He organized the young Marines around him. He identified enemy fire and redirected return fire. He directed his own medical care, including the application of tourniquets. He got the vehicles turned around and out of there -- all while going into shock.

Later, at Bethesda Medical Center, Major General Jones came to visit him, and Eddie was saying how he was lightheaded and realized he wasn't going to make it unless he took charge. General Jones asked Eddie, "How did you keep from passing out?" Eddie replied, "Sir, I couldn't pass out. I was in charge." Such is the character of our nation's warriors.

A little bit about why we need an HBOC in Special Operations. Our war fighters operate on small teams, deep inside hostile territory. Teams are mixed Navy, Air Force, Army, Marine Corps -- mixed up together sometimes on the

same team -- far from any established military medical support. What they have is frequently carried on their backs. Their missions last for days, sometimes weeks. If a member is injured, evacuation can take hours and sometimes days. They desperately need something like an HBOC. All they have now is crystalloid and colloid, not even oxygen.

Our requirements for an HBOC are pretty simple: It should be effective. It should be small in weight and have a long half-life, so that one or two doses would achieve the desired effect. It should be temperature-stable. We operate in a variety of environments and we don’t have any possibility for refrigeration. And it should be safe for our group of war fighters -- safe in our group of young, healthy individuals, without comorbid factors.

I thank the committee for its consideration. I would urge the committee and FDA to act expeditiously. Every month that goes by without an HBOC for our forces means that somebody is probably denied the benefit of this potentially life-saving therapy.

Thank you.

[Applause]

DR. SIEGAL: Thank you, Colonel Wright.

Dr. Colin Mackenzie?

Agenda Item: Colin Mackenzie

DR. MACKENZIE: Good afternoon, and thank you for the opportunity to speak to you today.

My name is Colin Mackenzie. I was the site principal investigator for the HEM-115 study at the R.A. Cowley Shock Trauma Center. I do acknowledge receiving funding from Biopure for this study and as an *ad hoc* consultant and chair of a company-sponsored medical symposium on Hemopure.

My background credentials are that I have used HBOC-201 in 34 patients. I am a clinical professor who has worked in the Shock Trauma Center for more than 30 years. I am well aware of the safety profile of HBOC-201.

[Slide] Based on this direct clinical experience, I believe that the product can be safely administered and is potentially life-saving in a RESUS study of uncontrolled hemorrhagic shock, such as is illustrated by this patient here, a 23-year-old Jehovah’s Witness who was admitted following being a pedestrian crushed between two cars near the Shock Trauma Center, sustaining fractures of the left iliac wing, left acetabulum, and separation of his sacroiliac joints and his symphysis pubis.

[Slide] You see that he also sustained a grade 3 liver laceration, had a pelvic hematoma, and bleeding from

both the right and left internal iliac arteries and his hepatic artery.

[Slide] His nadir of hemoglobin was 4.6 g/dl.

This slide has four important points. Point number one: The precipitous fall in hemoglobin here, despite resuscitation, a few hours after he was admitted, together with this rising lactate level, indicates that this patient was in uncontrolled hemorrhagic shock. As a Jehovah's Witness, he refused blood. He underwent angiographic embolization. I obtained consent, and using an FDA-approved compassionate use, we gave him 150 grams of HBOC-201.

The second point this slide makes is that HBOC is an acellular fluid. You see the rise in hemoglobin here and a fall in hematocrit, the additional benefit being an oxygen carriage from that increase in the acellular hemoglobin that adds to the existing red cells.

The third point that this slide makes is that the half-life of HBOC-201 is 19 hours. You will see that there is a progressive decrease in the hemoglobin. We need redosing in order to maintain the plasma hemoglobin concentration and the oxygen bridge that is required to maintain oxygen transport, due to this excessive earlier blood loss.

The fourth point that this slide makes is that

approximately one week after the point of administering the HBOC initially, we see this spontaneous elevation in hematocrit. Erythropoiesis results from the administration of HBOC. This patient received no blood. He was extubated on day 8 with a hematocrit of 24 percent. This spontaneously rose to 26.3 percent when he had surgery, percutaneous acetabular repair and fixation of his pelvic injuries. He was discharged on day 13, walking on crutches. He has resumed his activities of daily living six months later, except for the fact that he no longer does kick-boxing.

In conclusion, I would say that if it had not been for the infusion of 180 grams of HBOC in this particular patient, he would not have survived. I believe that the RESUS trial should be allowed to move forward because of the HBOC-201 product's significant potential to improve outcomes when blood is not an option -- the case in point being this description of this life-saving, compassionate use in a patient with uncontrolled hemorrhagic shock.

Thank you for the opportunity to talk to you.

DR. SIEGAL: Thank you, Dr. Mackenzie.

Our next speaker is Captain William Liston.

Agenda Item: Captain William Liston

CAPTAIN LISTON: Mr. Chairman and distinguished

members of the panel, thank you for allowing me to speak.

My name is Bill Liston. I'm a general surgeon who does trauma and critical care. I have no interest in the Hemopure company, or financial ties, nor to the Naval Medical Research Institute.

I am one of the guys that took care of that injured Marine. It's pretty tough to follow that, hearing what he said. For the past three-and-a-half years, almost four years, I have been taking care of the casualties coming back from Operation Iraqi Freedom. I do most of work doing that. I also had the opportunity to spend seven months taking care of the injured Marines up front at Al Asad, in the western part of the country, where all the action is -- besides Baghdad.

Also throughout my career, both as a civilian and a military surgeon, I have had an interest in trauma.

The most common cause of preventable death, which you have heard already, on the battlefield is hemorrhagic shock. Blood is difficult to store in a harsh environment, and it's difficult to give without precise administrative control. In the surgical company where I was, generally speaking, we had between 25 and 40 units of packed red cells at a time. When we had operations, we would replenish those supplies. But when we had bad weather and inability to get blood supply available, it was very

difficult to up those supplies to an appropriate level. In several situations, we went through more than 15 or 20 units of blood in a two-hour period, and began to use whole blood on a fairly frequent basis when somebody required more than three or four units of blood up front.

Having an off-the-shelf solution with oxygen-carrying capacity and colloid-like activity, with relatively low weight, not requiring refrigeration, not requiring cross-matching, would truly be a remarkable advance. I think we all agree on that. A blood-substitute product would provide additional resuscitation capabilities far forward to the medics and corpsmen that could be life-saving. You already heard that.

I have another situation that I recall, where there was a firefight and a sandstorm came in. It took three hours to travel six miles by Humvee. Two of the people expired from hemorrhagic shock because they had no blood available, no capability, no way to get it, and no way to get to me.

I think that if this trial turns out to be successful and there are more advances in this area, we could use this both at Walter Reed and at Naval Medical Center, Bethesda, and reduce the need for packed cells. I think this trial will allow careful follow-up while studying the usefulness of this product, with a good safety

profile. I think if there are adverse events, they will be picked up immediately.

This is a trial that cannot be done on the battlefield, because we just cannot do the monitoring. It's just impossible. But in an urban setting, this can be done, and it can assure safety. If there are any adverse effects, we are going to pick this up immediately.

Based on my experience taking care of these casualties here and over the past four years, as well as on the battlefield, I strongly would urge you to approve this trial.

Thank you.

DR. SIEGAL: Thank you, Captain Liston.

The next speaker is Emily Grushka [phonetic].

Agenda Item: Emily Grushka

MS. GRUSHKA: My name is Emily Grushka. Thank you so much for allowing me to be here and to talk with you. It's definitely an honor.

I am here largely because I was treated, very successfully, with Hemopure. While I am here at the request of Biopure and they did pay my travel expenses, I do want to make it clear that, had they not, I would have used every resource available to me to be here. It's extremely important to me.

I was 21 when I got sick. I was attending school

at the University of Washington, with a major in comparative religion. I still haven't figured out what one does with a degree in comparative religion, but there I was.

I presented with a petechiae rash and then was, shortly after, diagnosed with ITP -- not really a big deal. About a week and a half later, I passed out in my apartment and went back to the emergency room. This time I had no red blood cells, as well as no platelets. They started doing a lot of tests. It took them over two weeks to finally diagnose me, and they settled on Evans' syndrome. Evans' syndrome is a really rare blood disorder. It's found usually in small children. It consists of, basically, ITP and autoimmune hemolytic anemia, with a positive Coombs test. Essentially, my immune system was eating my blood. This became more and more of a problem with the more and more blood transfusions I was given, because my body would so quickly destroy all the blood that it was given.

In May, in a two-week time span, I received plasmapheresis, cyclosporine, a splenectomy and Cytoxan. Doctors were estimating that it would take a couple of weeks to begin seeing the results from these therapies. They did the splenectomy first and hoped that that would work and give them a little bit of time to do the other

therapies. The splenectomy had virtually no effect. So they knew it was going to take a couple of weeks for things to really kick in and they knew I didn't have that time.

I believe, at the time, I was up to 47 blood transfusions. I was becoming impossible to cross-match. My body wasn't getting enough oxygen. I was kept sedated to conserve the oxygen, but my major organs were beginning to fail. There just wasn't enough time, and the doctors began to tell my family to say their goodbyes.

Then one of my doctors, who was reading a canine magazine and stumbled onto an article about using Biopure's product Oxyglobin to treat anemia in dogs. Biopure was contacted, and the FDA granted compassionate use of Hemopure. I received 14 units over several days. Hemopure did exactly what they had hoped it would do. After the first unit of it, my hematocrit read as 4, which my doctor told me was not compatible with life, and I was sitting up talking to my doctors. Hemopure acted as a bridge. It carried the oxygen until the other treatments had time to reach effective levels.

It worked. It bridged that time. I believe it's the reason that I'm alive. It's also the reason that my family didn't have to say goodbye. It's the reason that I have a very beautiful four-year-old son, whose name is Logan. His ambitions currently include becoming a Ninja or

Spiderman or his Uncle Todd.

I am forever grateful to Biopure for the time that they gave me to live and to learn in this lifetime. I also now have a new motivation to keep an active interest in this particular product.

My little brother -- I suppose I can call him “little,” although he’s a lot bigger than I am now; he is still younger -- this year he joined the Marines. He chose to go into the infantry. In March, he will be sent to Ramadi. Last month, CNN elected Ramadi the most dangerous city in the world. My brother and his friends will be more likely to need medical assistance than anywhere in the world. The potential for Hemopure on the battlefield is unlike anything that we have seen. Knowing firsthand how Hemopure saved my life makes me excited for approval in trauma and battlefield situations. The next time, Hemopure could be saving the life of a soldier, maybe even my brother.

Thank you.

DR. SIEGAL: Thank you, Ms. Grushka.

Dr. Pruitt?

Agenda Item: Dr. Pruitt

DR. PRUITT: Dr. Siegal, Mr. Jehn, distinguished members of the committee, thank you for allowing me to attend this meeting of the Blood Products Advisory

Committee and offer these comments.

I am a professor of surgery at the University of Texas in San Antonio, professor of surgery at the University of the Uniformed Services here in Bethesda, and editor of the *Journal of Trauma*.

The resuscitation of severely injured men has moved from inadequacy, manifested by hypovolemic shock and organ failure -- principally, acute renal failure -- common in the mid-20th century, to the excess of recent years, characterized by compartment syndromes involving the cranium, the eye (both the optic nerve and the lids), and a variety of muscle compartments, and edematous compromise of the airway and the lung per se.

HBOC-201 offers the possibility of low-volume trauma resuscitation capable of minimizing or preventing tissue-injurious ischemia and at the same time, avoiding the complications of excessive resuscitation.

HBOC-201 has been associated with the occurrence of adverse events in patients of 50 years and more and an apparently dose-related increase in blood pressure and a decrease in capillary blood volume. Those concerns have been addressed by revision in the RESUS protocol, to a significant degree, by establishing 70 years as the upper age for elderly patient enrollment and by reducing the upper limit of systolic blood pressure to decrease

constriction of vascular beds.

It appears as if specific benefit may accrue from HBOC-201 in terms of maintaining cerebral perfusion pressure in trauma patients with traumatic brain injury. Those patients might well be defined as a specific subset for inclusion in the RESUS study.

In the aggregate, the animal studies of HBOC-201 indicate that the solution has the potential to provide clinical benefit in the RESUS trial. Particularly attractive is the finding of Knudsen et al., that HBOC-201 in small doses compared favorably with lactated Ringer's and hypertonic salt dextran resuscitation. That study has by some been incriminated as providing unequal shock protocols. But the relatively low salt content of HBOC-201, the least of the compared resuscitation regimens by a factor of 5, would have biased results against HBOC-201. The available preclinical and clinical data suggest that a treatment benefit of 15 percent reduction and relatively lower mortality may be achieved by the use of HBOC-201.

In short, I assess the potential benefits to outweigh the likely risks of the RESUS study for individual subjects, with the institution of the previously noted below-70-year, 120-mmHg-systolic-blood-pressure, and three-units-of-test-solution limitations. The potential likely risk-benefit ratio could be further reduced by limiting

study entry to patients below 50 years of age, for whom the odds ratio for cardiac death was indeterminate -- that is, no greater than any other limb of the study -- in an earlier study.

I was a bit concerned that one of the concerns voiced by the FDA was AEs and SAEs, and the age group that eliminated that -- they said they wanted to expand to the group that had those in it. I am really perplexed by that.

Additional monitoring techniques could address other concerns that have been raised. For example, near-infrared spectroscopy could be used to measure tissue and organ oxygenation status on admission to assess the significance of the HBOC-201-induced vasoconstriction. To decrease the number of study patients required, one could identify a narrower group or category of trauma patients with a predicted mortality of about 50 percent, which would permit the salutary effect to be identified in the smallest number of study patients.

In short, it is impossible to state prior to completion of the study whether entry into the study would benefit a specific patient. But the information available at this time suggests that surrogate decision making in a prehospital study is supportable.

Thank you.

DR. SIEGAL: Thank you, Dr. Pruitt.

If there are no further open public hearing speakers, I declare this open public hearing closed.

Is it the desire of the committee members to take a short break prior to resuming the open session?

["Yeses"]

Then let's do that. Let's limit it to 10 minutes, please.

(Brief recess)

Agenda Item: FDA Questions for the Committee

Open Committee Discussion and Recommendation

DR. SIEGAL: We have now as a committee to try to address the questions to the committee posed in this review, and hopefully that will engage people from the audience as questions are raised and as discussion proceeds.

The first question to the committee is, please discuss the following safety concerns raised by FDA, safety signals and adverse events in previous clinical studies, demonstrated vasoactivity of the product, and limited safety data for higher doses and rates of administration. Anybody want to start?

DR. FLEMING: Mr. Chairman, at what point will we have general discussion when we are going to bring forward

issues of discussion that basically is still background information related to preparing to answer the questions.

DR. SIEGAL: We could do that first. I think that is perfectly legit. So, if you have something to generally discuss, go to it.

DR. FLEMING: There are several issues that I have been trying to best possible -- its best possible understand, based on the evidence provided by the sponsor and the evidence provided by FDA.

Part of what is motivating a series of questions that I have or analyses are the conclusions that were put forward in Dr. Freilich's presentation, which I found very informative, and yet I am struggling with the strength of some of these conclusions. These are on slides 193, 194 and 195.

Just to quickly enumerate these, he noted that there is a 75 percent reduction in mortality expected from the animal trials, and it is conservative, in essence, to assume a 15 percent reduction, which is five-fold less.

Yet, for reasons that have been discussed many times relating to the heterogeneity of the population where issues along the lines have been stated, most will die, or

most will survive in ways independent of the specific 201 versus LR regimen that is delivered, if that is true, then that has a huge impact on what is a truly plausible effect that you would see in a RESUS trial.

In essence -- and I don't know the extent to which the population is in a setting where they would inherently survive under either intervention or inherently would die under either intervention, but it is that middle ground that can be impacted.

One comment that I think is not relevant to this context this morning put by a trauma physician was that 96 percent of the patients will survive, three percent of the patients will die. It is that one percent that we are really going to be able to do something about.

Well, hopefully it is more than one percent in this trial. If, in fact, of the 58 percent who die, hypothetically, if it is as many as 40 percent that are going to die independent of what you do, and you have the death rate in the remaining patient, that is just a 15 percent reduction. So, that is a 50 percent relative reduction in those people in whom you can do something.

I don't know the answer, but it seems very

aggressive to say that we are being highly conservative with a five-fold reduction when we are presuming a 15 percent relative reduction when the animal studies state a 75 percent reduction.

There were additional conclusions -- five, six, seven, eight and nine -- that set the stage for a few other issues that I wanted to better understand.

One of those issues is that the statement was made, if we go to the younger population and people who are less than 70, that narrows or, in fact, leaves non-existent safety signals, which is a very strong statement for the level of interaction that age has with the safety risk.

Other statements were made that there is only a mild adverse shift in the safety profile. Another statement that was made was, the South African study provides indications of an improved safety profile.

Then, quantitative analyses indicate a highly favorable benefit to risk. So, there are very strong conclusions being drawn about the nature of the data.

As I look at it, there are roughly three or four or five issues there. Taking them one at a time, age, there was a lot of discussion earlier today about how

generalizable should the eligibility criteria be.

My own philosophy is we should be inclusive to allow a generalizable result, and be restrictive only to the extent that prior data provides considerable insight that certain types of patients wouldn't, in fact, be as likely to have favorable benefit to risk as others. If that evidence is there, it makes sense to exclude those patients.

The argument, therefore, would be that over 70 should be included unless there is considerable evidence that they are at much less likely basis for getting favorable benefit to risk.

When one looks at the data, while it was stated on slide 194 that, by going to people younger than 70, that narrows or renders non-existent excess safety risks, these excesses don't seem to be -- the reduction or the association of risk with age doesn't seem to be striking.

It is 7.7 percent excess numbers of people that have an SAE overall, 6.1 percent by the sponsor's own analysis in people less than the age of 50.

One table that I will refer to several times that I found very informative is the FDA table 3.B on page 51 of

75, and I will be referring back to this several times.

In this document, if you look at the totality of data that we have in the available 1,400 people who have been randomized to this point in control trials looking at HBOC 201 versus control, what we find is, in those people that are below aged 70, by my count the percent of people that have at least one of these clinically significant AEs is increased from 6.2 to 16 percent in the people below 70. It is 25 increased to 43 percent in people above age of 70.

That is not a striking difference in terms of the relative increase in safety risks in people above age 70 compared to people below age 70.

In essence, subset analyses are inherently extraordinarily difficult to interpret unless there is a very, very compelling interaction.

As I look at this, it sounds overstated, and I think the FDA came to a similar conclusion, to indicate that we can largely reduce, if not eliminate, the safety risk by excluding people over the age of 70.

The next issue comes to, what are the sources of information that we have for efficacy and safety. Predominantly preclinical data the 0115 trial, and the 0125

trial.

When we look at preclinical data, Susan Sterns' conclusion was, one of her conclusions, was that HBOC 201 did not result in indications for significant increases in morbidity.

Dr. Freilich's presentation, on slide 153, indicates that mortality would be dramatically reduced. He goes on to say, on slide 156, that preclinical data indicate no evidence of increase in heart failure or cardiac injury.

Yet the data that exists, if we look at this table 3.B, FDA's summary on page 51, the totality of these data indicate that there is a one-and-a-half fold increase in the totality of data in death rate, three-fold increase in MI, two-and-a-half fold increase in cardiac arrest, two-and-a-half fold increase in heart failure.

Those are all, in fact, domains that we were told the data from animals indicated we shouldn't have an increase.

So, can we trust those data to indicate that, in the rhesus trial context, there won't be an increased risk when I presume before we would have done the 115 trial, we

would have been somewhat reassured that these data should have indicated in that context there wouldn't be an increased risk.

Nevertheless, there was an increased risk. As was pointed out in the open public hearing, this increased risk, when you look at totality of events -- and these aren't just adverse events. These are the kinds of significant adverse events that very often carry significant long-term morbidity with them.

These death, MI, cardiac arrest, heart failure, cerebral vascular events, stroke, dialysis, renal failure, there were, in the totality of the 708 people who were on the HBOC regimens, 172 of these events compared to 72 in 618 such people, that is an increase from 11.6 or about 12 such events per 100 people to over 24 such events per 100 people. This is an excess risk that exists in both of the contexts of red blood cell and crystalloid controls.

Essentially, as we look at these data, then, it leaves me with a lot of uncertainty as to if these data didn't accurately predict the excess risks that we know occurred in 115 and overall in these 1,400 people, what is the basis for judging that the lack of excess risk in

animals will apply in the rhesus trial setting.

Analyses were done based on looking at excess SAE scores, ESS scores, and there were three different analyses that were presented.

Actually, the analysis that was shown to us today, analysis two, is the one that I actually found the most interpretable and informative.

In essence, it doesn't try to put a score on how important these clinically significant AEs are relative to death.

It is very appropriate to recognize that, on average, preventing a death would be of greater clinical significance than inducing one of these events, but it is extraordinarily difficult to put a score on exactly how that compares.

So, what this analysis basically does is looks in essence per 100 people at how many deaths are prevented versus how many of these events are induced.

While there is some assessment put forward, basically, according to what was presented to us, scores that are better than one to one would be highly favorable. That is where you are preventing at least one death for

each event SAE induced.

Once you get to about three to one, it becomes vague as to whether that is positive or negative. That is essentially what was put forward.

The conclusions that were reached on this is that the data indicate we will have a highly favorable benefit to risk.

That is based on an assumption that you are going to have approximately 5.9 of these events induced per 100 people, and you are going to prevent 8.7 deaths.

So, it is based on this assumption of a 15 percent relative reduction in death rate with a 58 percent background death rate, which is .7.

If that would be true, I know I would feel greatly reassured, because it does seem to be that that is a very favorable scenario.

Well, the 5.9 is presuming that age is truly a validated effect modifier factor, that it really does mean that the 7.7 estimate overall would be reduced to 5.8. That is unclear.

The other aspect of this is, if I look at the FDA's presentation of the totality of the data from the

1,400 people that have been randomized, I don't come up with 5.9 or 7.7. I come up with 12.7, 12.7 of these events like stroke and MI, et cetera, per 100 percent years.

The other issue is, 8.7, which is the positive side, deaths prevented, isn't the result that will yield statistical significance.

The result that will yield statistical significance is only 5.8. So, while the projections all day today have been a 15 percent relative reduction, which is 8.7 fewer deaths per 100 person years, is what the study is powered for, this study will achieve statistical significance, two-sided 05, with a 10 percent observed relative reduction, which is only 5.8 deaths prevented.

To me, now, this is a different picture than what the sponsor was presenting in their summary slides. I am not making a judgement yet whether it was unfavorable, but it is a different picture.

It is a picture where there could be, based on FDA presentation, 12.7 of these serious clinical events induced, and only 5.8 deaths prevented, even if this result is statistically significantly positive, which is an excess SAE score of 2.2.

That is if they achieve statistical significance, they are still at 2.2. Now, there is still judgement as to whether that is adequate.

That is a very different picture than saying the data are projecting that you should expect from the data presented that you are going to have more deaths prevented than serious clinical events induced.

Another key point is, the other source of data is the 0125 trial, and this is the South African trial. This is a study of 50 patients.

The data were presented to us on 19 patients, and there were eight deaths. If it were left at that, I guess I wouldn't have significant concerns, but it wasn't left at that. I have two significant concerns.

The first is, in Dr. Freilich's slide on page 135 and 137, there is a statement that, we have equivalent mortality, equivalent mortality when we have eight deaths. We have observed -- I should reiterate -- eight deaths in 19 people. Because they were four/four, the sponsor conclusion is, we have equivalent mortality.

Anyone involved in a non-inferiority world would be apoplectic hearing such a conclusion drawn on such

paucity of evidence.

Just to put this into context, if you wanted to discern whether or not this intervention doubled the odds ratio for death -- so, whether to discern between such striking differences as 40 percent mortality not increased at all, 40 versus 40, versus a doubling of the odds ratio, that is 40 versus 64, which would be a huge increase in mortality from 40 to 64, it takes an order of magnitude more deaths than that. It takes about 80 deaths to discern that.

So, these data, while extremely small numbers, is encouraging, because you are not seeing any difference, there is essentially no evidence here in this context. These data are consistent with a seven-fold increase in relative risk, based on this.

The other aspect that is concerning to me is that we were informed that this is a study that is ongoing, where the data monitoring committee indicated the study should continue.

Unequivocally to me, having sat on many, many a monitoring committee, is an indication from the committee that this study has not addressed the questions that it was

designed to address.

I have scientifically and ethically serious concerns about the inappropriateness of the revealing of confidential interim data to the sponsor, to the FDA and to this committee, because it significantly compromises the integrity of an ongoing study. Furthermore, it is presenting results that are obviously incredibly unreliable.

So, we are left with an extraordinarily unreliable source from 0125 that was inappropriately unblinded. We are left with animal data that inaccurately predicted the safety risks in 0115, and we have to use that for the context of the RESUS study.

We have data from what the FDA has presented to us in the totality that suggests it might be closer to 12.7. Now, we asked them, and we don't know, does the result from previous studies extrapolate to the context of RESUS.

That is uncertain, but those data indicate 12.7, which is more toward two to three events that are occurring per life that might be saved.

Very quickly on two or three other quick issues,

I will make little of this issue, but there were some attempts made to reanalyze the 0115 data in the materials presented to us, looking at subgroups of people that might be viewed as less seriously ill.

Those analyses are using characterizations of what happened to people post-baseline. Did they get RBCs. Did they get less than three units of RBCs.

Those are treacherous analyses. They have lost integrity of randomization. They are tempting to look at, but they don't allow you to reliably discern what is treatment effect from selection factors of people who are inherently worse off in the first place, that led them to have certain results.

DR. CRYER: Tom, could I interrupt you on that? Are you talking about the data the FDA presented on the complications or the company?

DR. FLEMING: There were some analyses for both, although not much was made of them today, but more in the briefing documents by the FDA and the sponsor, to try to glean more insight from the 0115 trial about people who were less seriously ill.

So, we have the groups called the HH group and

the R and the HR groups, all of those analyses. While they are well motivated, the problem is that you have lost integrity of randomization when you start doing -- we call them subsets, but they are not subsets.

A subset must be based on a factor that is known at the time of randomization. If it is only known after randomization, you are going to get inherently biased comparisons, and it is unclear whether the differences are now due to the intervention or due to the selection factors of who was inherently worse off in the beginning.

On slide 37, Dr. Dutton presented an issue relating to the informed consent, but that is somewhat shifting here gears. Should I go on to that, or did you want to pause?

DR. SIEGAL: Does anybody want to discuss what has been raised already or would you like to summarize?

DR. FREILICH: Mr. Chairman, is it possible to get a clarification for just a minute? Thank you for those comments.

We actually have a bunch of comments that we would like, if possible, to provide when you think is practical about some of these issues, but we have a

question.

We really just don't understand the 12 percent, Dr. Fleming, where that is coming from and, if possible, we are hoping that a clarification might be available.

DR. FLEMING: I would be happy to. I will do it very quickly here. If we go back to the FDA briefing document, page 51, table 3.B, the FDA has presented -- they presented about eight to nine categories of what were listed as clinically significant AEs.

Dr. Silverman today presented some slides that were similar, not exactly the same as this, but very similar.

If you look at the totality of the events that occurred, if you are basically looking at these first four columns and you are looking at totality of events that occurred on the HBOC 201 and the control, and you sum across these categories, what you are getting are 172 events occurring in 708 people versus 72 events occurring in 618 people, 100 excess events, although there were slightly more people.

That breaks out as 24.3 events per 100 people and 11.6 events per 100 people. It is one of the approximations

that can be used for approximately how many excess events of these types are occurring per 100 people.

This is based on the totality of the data that exists that has been put forward in phase I, II and III trials, more than half of this coming from the 115 trial, and the results in the 115 trial are quite consistent with the other data from outside the 111 trial.

DR. FREILICH: Would it be possible to address this now that I know where it comes from?

DR. SIEGAL: Yes, please, but go to the mike.

DR. FLEMING: Just as a quick aside, I am happy to have this addressed. I am just worried about, since it is now 4:00 o'clock and the committee is now just getting its opportunity to query, if the sponsor is going to continue, if they could be very concise.

DR. FREILICH: It will be very brief. Our understanding of the SAE difference in the ISS is five percent.

When one takes that table and you combine AEs and SAEs, in fact that table doesn't even tell you if it is AEs or SAEs. It just says, if I recall, clinically significant, and then there are things such as et cetera.

One doesn't actually know what you are looking at. In fact, many patients have SAEs twice. So, a patient who had an MRI may have a stroke.

What you end up with is somewhat, in our opinion, a misleading view. I think what is purely fair is that the overall SAE rate in the 115 trial was, as enumerated earlier, almost eight percent.

If one wants to look at the overall ISS to take into account the phase II trials then, in addition, it is very similar to that five percent. Counting things two or three times is somewhat unfair in terms of understanding benefit risk.

I wanted to comment about age. There is no question that NMRC understands that some of the diminished group differences as you look at age are related to the fact that you simply have lower event rates, but it is not all that.

In fact, as is in your package, some of the logistic odds ratios are very, very dramatically lower when you look at the lower age populations, in fact, as low as sometimes .12 or .2, in very, very significant SAEs, in fact, the one that I am most concerned about, which is

stroke and cerebral ischemic AEs.

So, it is possible that, when you take overall SAEs, age restriction is not going to diminish every one, but it is going to diminish the significant ones and many of them, such that the overall benefit risk ratio is significantly improved. I thank you for your time.

DR. FLEMING: Let me clarify. Basically, if you go on to pages 52 and 53, you do get the specific breakdown as to which of these events are AEs and SAEs.

Because of the seriousness of these clinically significant categorizations, in most of these categories, most of the events are, in fact, also listed as SAEs.

Secondly, I was very careful to state that this isn't numbers of patients. This is numbers of events. Partly, we haven't been given numbers of patients.

The reality is, if you induce an MI and you induce a stroke in a person, that is not the same as just inducing one or the other.

So, an analysis that just looks at numbers of patients is underestimating the clinical significance of side effects if, in some cases, you had a stroke and an MI.

So, I intentionally was presenting it exactly as

it was provided. This is the number of these serious excess events that, in excess, would be induced by this therapy per 100 people.

DR. HAUSER: I think it is important to recognize that, in the patients that we are looking at, really, which is the young trauma patients, the ones that we are really concerned about, neither strokes nor MIs ever happen.

So, predicting that they are going to happen on the basis obtained, for instance, in elective surgery done in orthopedics patients, most of whom are probably volume replete, hemoglobin replete and intolerant of both overload and afterload, is not going to reflect what is going to happen at all in the younger patient population.

These just -- as you put it, they will not extrapolate. So, I think that it is very difficult, and probably we should not be looking at that. I don't know which the number of that study is.

We probably should not be looking at that at all as a predictor of adverse events in the young age population.

Now, I will accept that that probably is a pretty good predictor of adverse events if we were to use the

older age population, allow that population in the RESUS trial.

DR. FLEMING But as you just look at the data in table 3.B from FDA where there is not a striking difference by age, you would not use the younger age patient data there. What would you use? What would you use to understand safety risk if these data aren't, in fact, at all informative.

DR. HAUSER: I am not sure that there is anything that we can use.

DR. SZYMANSKI: I would just like to comment on the same table, 3.B. If you look at the two age groups, 69 years old and more than 70 years old, and you look at the controls, and if you calculate the percentage, so the controls already are very different.

Over 70 years old, they go from 08 to 5.5 percent. They are not here indicated as percentages, but I calculated in my sort of head, not using a calculator, but they definitely are very different, just even the controls. Therefore, I think the older age group is really more susceptible.

DR. FLEMING: It is a gray point, but just to