look -- you are right. Now you are looking at, on this page, the four columns on the right.

You are absolutely right. If you look at the controls less than 70, there are by my calculations 6.2 events per 100 people.

The controls greater than 70 have 25 events. That means age is a predictor. The older you are, you do have a lot more events.

That is a separate issue from what we are most concerned about. Is age an effect modifier. Is the treatment induced increase in risk specific to age.

So, while age is a predictor, you are right, there are six events per 100 person years in the younger patients, 25 in the older, treatment is inducing increased risks in both groups, increasing the 25 to 43 and increasing the six to 16.

DR. SZYMANSKI: Even if you look at the Delta numbers, they are larger for the old age group.

DR. FLEMING: The delta isn't 25 to 43. The delta is 18.

DR. SZYMANSKI: I am just looking at the percentages. The hemoglobin versus the control, delta, is

higher in every category.

DR. FLEMING: The absolute increase is somewhat higher. The relative increase is much higher in the younger patients.

DR. SZYMANSKI: No.

DR. FLEMING: Yes, it is. Sixteen to six is a relative risk of 2.6. Forty-three to 25 is a relative risk of 1.78.

DR. SZYMANSKI: But you see the total number is much less. In the over 70 years old, it is 222, whereas in 69 and less, it is 076. Therefore, if you take a percentage, then you can properly evaluate these two groups, not as absolute numbers.

DR. FLEMING: The bottom line here in these four columns is that age is very much a predictor. The rates are much higher in the control groups in older patients, but there are substantial increases by intervention by HBOC versus control, in both age groups.

DR. SZYMANSKI: Yes, but more in the older, definitely more.

DR. BUCHMAN: I want to caution the committee on getting too deeply hung up on specific adverse events. As

Dr. Cryer and Carl mentioned earlier, the patients with whom we are discussing today are patients who are in deep shock and who, without the most aggressive forms of care, would not survive.

When we do have a survivor of someone with this depth of trauma and associated hemorrhagic shock, it is common that we see pneumonia, it is common that we see significant renal insufficiency requiring dialysis, and the rates at which we see these types of complications far exceed the absolute incidence of these findings in the elective population young or old.

It is true that, as our trauma patients age and they have this severity of injury, yes, we will periodically see patients who have myocardial infarction and possibly stroke, possibly as a consequence of their injury, sometimes as a consequence of their treatments.

The types of differences that we are talking about in the elective environment are completely washed away by the ordinary frequency of these events in the population that is going to be the target of the RESUS study.

DR. PICKERING: I would like to make also a

comment about table 3.B. Dr. Fleming is a statistician and I think focuses on the numbers, but for clinicians, I think they look very different.

I think there is one event we can all agree on is really critical, and that is death. When you look at some of the others like congestive heart failure and pneumonia, I don't know how to interpret them in this context.

I suspect if, for whatever reason, people get over-transfused, they could be diagnosed as having congestive heart failure.

Whether it has the same significance as long-term congestive heart failure -- the same with pulmonary edema. These are all potentially transient things, and I have no way of knowing whether either of these are going to be life threatening over the long term as a result of having had the hemoglobin OC transfusion. I am not too impressed by this table.

DR. FINNEGAN: I would like the sponsors to address both the definition of life threatening and the EMT situations in this country.

EMTs across the country have levels of expertise that vary from none to shock trauma. The RTS scale requires

some sophistication and it also requires some subjective decision making.

The ATLS scores are much more objective. I am wondering if you could discuss, first of all, how you are going to discern which EMTs you use and which standard of training, what level of expertise and, secondly, how you are going to define life threatening.

At least in my world, the EMTs are going to be very excited, A, that they have something that they can give and, B, that they are going to be part of a very famous study.

So, the indications for giving this are going to be sort of pushed. That is where the study and the material is going to run into trouble.

As someone mentioned earlier, if that happens and the New York Times gets it and the Washington Post gets is, we are all put back about 20 years. So, can you discuss that?

DR. FLEMING: With respect to selection of trauma centers, in this trial you can select those trauma centers, and what you are alluding to in terms of EMS, systems that a high quality is required also.

Number one, pretty exclusively, we use level one trauma centers only. Number two, within the level one trauma center, what we do is, we collaborate and we sit with the local PI and the local EMS directors and we figure out which EMS systems, two-fold, number one, have a high mortality rate.

There is no point in training people who are going to end up enrolling someone every two or three years. You will have bad outcome and bad results. Secondly, you need high quality, you need paramedics, you need EMTPs, you need EMTIs.

In general, we don't accept EMT basics. There are possibilities of exceptions. At the University of Vermont, for example, it is possible, if Shackford can show us that the EMS group there has the capability, despite it being a volunteer-type EMS, we might make an exception.

The plan in general, for almost all of the trauma centers, is that you down select specific EMS systems that have the capability.

Secondly, there is a very comprehensive training program with repeat training. As you alluded to earlier, there is an incentive to enroll, and we want to prevent

that from happening.

I think you asked a question about life threatening. Is the question that you are getting to that they may end up enrolling people in less than 10 to 15 transportation times?

DR. FINNEGAN: No, the question is that they will be enrolling people that really aren't life threatened, that probably would survive.

DR. FREILICH: Paramedics are like military, and they follow protocols. Every EMS director that we speak to -- in a moment I am going to ask Mr. Aker to get up for a moment -- there are specific inclusion criteria.

They need to look at the blood pressure. They need to add the RTS, and they need to look at the remainder of inclusions.

They don't need to make a decision if the clinical situation is life threatening. The numbers will answer it for them.

DR. FINNEGAN: With all due respect, the reason we do so well in some war games is because the military don't follow directions and neither do paramedics in a lot of instances.

DR. CRYER: I would like to comment on what Dr. Fleming was talking about. I think I have to agree with his assessment that there is a lot of uncertainty here.

I guess the only way that I can put it together is that it makes a compelling argument that we need to do a prospective study to learn, if nothing else, how to do these trials.

Right now, nobody has actually pulled one of these off that was successful. We desperately need to be able to know how to do that.

I think that it would be nice, as the FDA said earlier, that we got some phase II studies with consent but, as the young woman told us who got stabbed, when they asked her and tried to get consent she said, look, I am stabbed and in shock, I don't know what to do.

Even if she said yes, it wouldn't be informed consent. It is absolutely impossible to do that. So, somehow we are going to have to be able to validate the group that is the study group.

I will tell you that there are a couple of ways that you can do that in patients within the hospital data. The GLU grant comes to mind.

All of those predictors are on things you know after the patient already gets to the hospital, you have already resuscitated them, you already did the CT scan and you know what the injuries are.

These patients are out in the street, shot, lying in a pool of blood. You don't know how old they are. You don't know anything about them and you certainly can't get consent from them.

These patients, I am not aware of any study that has actually validated criteria with outcome and even what you did with the NTDB, it is hard to know the accuracy of the data that is in the field

That NTDB data is collected in the emergency room. So, we don't know. That is the bottom line. We either need to do some study to try to define that group better or say, let's go ahead and do it.

I couldn't agree more that there is a lot of uncertainty here. I just don't know how to get around it without doing it.

DR. HAUSER: I just want to, I guess, ask the sponsor why do we need to do RTS anyway. What is wrong with blood pressure and patients in clinical shock. That is

question number one.

Number two, if there are -- there are clearly -- every clinical trial has incentives to do the trial, and that sometimes will drive what I call non-righteous admissions.

Are there disincentives built into their study, that you can take centers that enroll non-righteous admissions and take them on out?

DR. AKER: Can I possibly answer a couple of the EMS issues for you? One of my responsibilities as a regional EMS director is to take the barriers away that allow the paramedic to do the right job, and put barriers in the way of doing the wrong job.

We do that through a quality improvement mechanism where we look at patients as they are enrolled. There is such a study, somewhat similar to this study, that is in place right now, and that is the resuscitation outcome consortia, where hypertonic saline is being given, and we are one of those sites.

We have to, as EMS providers, make those decisions today. One of the things that we do is, we do good education.

Number two, we provide to paramedics, while the paramedic is at the patient's side, the ability to look at a card and read through.

That doesn't help if it is 3:00 o'clock in the morning on the side of the road and you can't see your deal. So, how would I deal with that as an EMS system director? Trauma communication center, this is BRMS II.

[Radio transmission played.]

I have a patient with a glass coma scale score of 7. I have a blood pressure of 69 palp, and I have a respiratory rate of 6. Would you give me an RTS, a revised trauma score, on this patient.

[Radio transmission played.]

I am talking from here to Birmingham, and by golly, if I can talk -- some people made statements about the ambulance I put up there and they said, I don't want to be in Alabama, but if I can talk from here to Birmingham to a trauma communications center, and I can get a revised trauma score that easily in process -- and they didn't know I was going to call --

[Radio transmission played.]

I copy. This patient will be enrolled in the

study. That is the way it works.

DR. FINNEGAN: But it is Saturday night and that person gets 15 calls, that is not going to work so well.

DR. AKER: I have got two people on duty. I put 4,000 patients a year in, and by golly, the paramedic in the field, when they make that call, is first priority and we are going to make it happen.

DR. FINNEGAN: What we are trying to do is make it clinical hypovolemic shock, which is numbers, just absolute numbers. There is no decision making and that will give you the purest --

DR. AKER: My point to you is, you design what you want. We at EMS are going to make it happen.

DR. HAUSER: Which brings me back to my issue. What are we using RTS instead of just hypotension?

DR. FREILICH: Sir, RTS was added for two reasons. First, it was actually at the recommendation of the FDA, which I think appropriately critiqued the initial resuss design, which mainly relied on blood pressure, systolic, under 90.

It is true that, if you use systolic under 90, which really is the main inclusion criterion of most trauma

trials, you end up with a relatively low mortality.

FDA recommended inclusion of RTS because, appropriately, there have been studies which have shown that you can use it in order to target a population. Secondly, it has been shown in prehospital setting.

The issue is that you can, in theory, simply use a lower blood pressure, and I think that is what you are getting at. In fact, the ROC has done that.

One could do a combination. The problem with hypotension alone, for example, you can pick an SBP of less than 75, and we ran that through all these trauma registries.

What you end up with is, you have certainly dropped the mean mortality. The problem is that you still get that heterogeneous U-shaped distribution. The RTS gave us a relatively reasonable -- and I understand that reasonable is relative -- distribution.

DR. SILVERMAN: May I correct the record here? At the pre-IND meeting, NMRC proposed an RTS greater than one. We discussed the REU paper that has been alluded to and we suggested putting an upper limit on the RTS, but we did not recommend the RTS.

DR. KULKARNI: As a pediatric hematologist and as somebody who works with trauma surgeons, I can tell you that looking at all these trials, especially the HEM 0115, my conclusion is that this drug is terrible for a 70 year old man undergoing orthopedic surgery.

Having said that, I have to think about the 58 percent mortality that was presented on the field. I am trying to figure out how these two go together.

Whether we like it or not, we have to take into account the data from South Africa. I think we can't just ignore that.

So, on one hand you have patients who are dying in the field. On the other hand, you have old people getting all these adverse events, and some young people, but it is a different setting. So, I think the setting is so different, it is very confusing.

DR. SIEGAL: That really brings us to the first question, so let's just discuss it up front, if you don't mind.

DR. FLEMING: Just two other very quick issues before we go to the questions. One of them is, we were presented today slide 37 by Dr. Dutton, who was taking us

through the process of documentation of benefits and risks that would be read to participants.

There was an explicit statement there that I recollect -- I don't know if slide 37 is easily available -- that basically says, doctors believe that benefits outweigh the risks.

I have a significant concern whether that is an objective presentation of what we actually know. There is a difference between plausibility or hope that benefit exceeds the risk versus an expectation.

As was mentioned in the open public hearing, ultimately randomization is based on a principle of equipoise, where there is yet substantial uncertainty.

I have got concern about an informed consent that is specifically stating that doctors believe that benefits outweigh the risks, instead of a statement that there is plausibility and yet there remains substantial uncertainty, hence we are randomizing you to these interventions.

On a quick second issue, although I am not sure how quick it is, I have been struggling all day with the issue of generalizability.

We heard at the beginning of the day from the

admiral that, at least in many sectors, a great deal of interest in the results of this trial relate to military contexts, and specifically Operation Iraqi Freedom.

Yet we have been hearing a lot about what the realities are on the battlefield and, in the safety profile, about the length of time between when you could be randomized and when you could actually get access to RBCs being really critical.

If this study is done in an urban trauma context, does this truly allow for generalizable conclusions to the context of the military, that this is, in fact, going to yield results that are satisfactory? Is this ethical?

Is it ethical to do a trial that will, in fact, be used in a decidedly different context, where benefit to risk could be very different, and yet there weren't any attempts made in the prospective planning of that trial to try to get an appropriately generalizable conclusion.

As an example, when our cardiorenal advisory committee was considering VITAL now, some year or so ago, there was considerable discussion about the appropriateness of labeling that intervention in blacks only.

Yet there was an explicit restriction to allow

only blacks into the trial. Many of us said that the label should match what it was that the sponsor had in mind when they, in fact, specifically designed and conducted the trial.

Is it, in fact, correct to say that the military realities as to how this product would be used would be distinctly different from an urban trauma context?

If so, and if these data are all that we are going to have to make a judgement in the military context, is it in fact appropriate to go forward without including some evidence in here.

While it is obviously going to be a different challenge to conduct a trial in that setting, isn't it possible to do group randomizations where you are randomizing units or some other entity to A versus B, and you are going forward and at least being able to assess survival and very significant clinical complications?

Is it truly impossible to get a result that would be adequately generalizable to the context where the questions remain unanswered?

DR. SIEGAL: In a military setting, is what you are asking.

DR. FLEMING: Yes. Is it truly impossible for us to do more -- is it impossible for us to be able to get more insights into the extent to which this trial, RESUS, if it is done, is truly relevant to the context to the military setting where obviously, from all the discussion today, there is a clear indication that there is keen interest in being able to use this product in that context.

DR. CRYER: Can I address a little of that? One option, I think, that we could do is recommend that we just let the military go try it like they do other things.

I mean, they did that with factor VII-A. They did that with Ringer's lactate solution in a previous war, and we adopted it in a civilian setting with no trials whatsoever. They just tried it and it appeared to work. So, they kept doing it.

Now, the problem with the military is exactly that. We didn't really learn anything about whether the control group, now, in our current standard of care, which is Ringer lactate, we didn't learn anything from all of that, because it wasn't done in a study format.

So, they could do a trial and maybe that would be the way it should go. I don't know. If they do, they are

not going to learn what we would learn by doing a prospective randomized trial here and collecting data and being able to have valid control groups and get the risk factors and all the things that you were saying were uncertainties a minute ago. I feel like that is probably not the best approach.

DR. HINTZE: Just sitting here listening to this, we are talking years away before this will be applicable to the battlefield or to a military setting. This is on the record here now as a concern. Can't we revisit this some time in the future?

DR. HAUSER: I think it is also important that we can structure, or we can recommend structuring the current ongoing trial to reflect those realities in the battlefield more closely.

For instance, I think the point is well taken that true urban casualties coming in within a few minutes probably do not reflect the bulk of the events that occur in the military scenario.

More suburban and rural transport might well be a better predictor of the results in a military setting. We could recommend going in that direction, again, limitations

to younger populations that more accurately reflected the military cohort.

DR. KATZ: Mobile(?) seven came to my mind, as it obviously to many other people on the committee. My understanding is that the military got access to that because it has got a labeled indication and you can go out and buy it from the wholesaler. This HBOC 201 has no label indication. So, it really isn't available.

I asked several of the military here whether they can do a trial appropriately powered with one end point, that being mortality, survival to the MASH unit or some point after that.

I am told, without a lot of detail, that there are regulatory barriers to that approach, a study with so few end points. I would like to hear from the FDA about the military.

DR. EPSTEIN: We are not at all averse to a dialogue with navy or other components of the Department of Defense about trials in the military theater.

We tend to think it is the best way to get the most relevant data and that simply trial designs could potentially be brought forward.

I wouldn't say that these are regulatory barriers, only that they are regulatory considerations. In other words, you would want some type of suitable control and you would want some useful outcome reporting, but these are things that can be discussed. We do have an open mind and, indeed, we would encourage a dialogue of that sort.

DR. KATZ: Jay, I meant regulatory considerations

DR. CRYER: If I might make one other comment, too. You know, one of the things that strikes me, one of the problems they have is, they don't have enough injuries.

As embarrassing a statement as it is, and social comment, we have far more badly shot up and hemorrhagic shock patients in the United States than they do over there in Iraq.

So, the number of patients that we can study here are a lot more. I think that actually we talked earlier about it, there is a compelling argument for including only penetrating trauma, as Dr. Demetriades suggested.

There are a lot of places in the United States in urban settings that are analogous to the combat zone, in that they are combat zones.

It is not so much that it takes a long time for

the paramedic to get the patient to the hospital, but it oftentimes takes a long time for the paramedic to get to the patient because it is not a safe area for them to go into.

I don't know. I think another option would be that it would be a more convincing group of patients that would be analogous to the military situation and probably have a better chance of being effective overall in a study design if they were penetrating only.

DR. FINNEGAN: I actually had considered another option. It strikes me as, I don't know -- I am Irish Catholic, so not right sounds like a good term -- that we can give this compassionately to a 23 year old in Baltimore, but we can't give it to the kids who are trying to protect us from bad people.

So, is it possible to do a compassionate care to the military with the proviso that they can track the mortality of the people that got it.

DR. SIEGAL: I have a question actually. I understand that there was a compassionate use trial of HBOC 201 and, in fact, one of our anecdotal speakers described participation in that trial.

I wonder what happened to that trial and what the experience was, if there are any data about that. It would bear on the question of using it in a compassionate use setting in the military.

DR. SILVERMAN: Can I correct that? There were a number of emergency INDs under which the product was used patient by patient. Biopure would have the information about the outcome for all of the people who received the product under that program.

DR. FINNEGAN: This would be giving it to the military so they could use it in the field, not that they would come back patient by patient to ask for it.

PARTICIPANT: Can I address some of these military issues?

DR. SIEGAL: Yes, please.

PARTICIPANT: The military is not as homogeneous as somebody might imagine. Dan and I have argued about this behind the scenes multiple different times.

The simple fact is, we can't even get all the medical records back on each individual. So, collecting usable data from the battlefield is enormously challenging.

I would have the fears Gil just mentioned, that

we would collect useless data in that situation, not prove the point and potentially have a negative impact of people damning the product for some bad outcomes not related to the episode.

We just simply cannot get that data off the battlefield, as mentioned poignantly today by the people under fire trying to deliver the care. So, I would resist it.

Part of me would love to do it, but I would resist it. Dan and I in a closet have beat each other up for that multiple times because we would love to get that kind of data. We would love to have the heart to do these things for the soldiers.

The nation told us in the last war in this theater that we will not tolerate soldiers being guinea pigs. That came through loud and clear, and that is what will happen.

DR. MICHAEL: Could I just say something about that also? My name is Rodney Michael. I am with the army medical materiel development activity.

About two years ago we attempted to get an IND protocol for putting HBOC on the battlefield. Our special

forces medics ultimately decided that they couldn't manage the accountability associated with an IND product. So, we stopped the protocol at that point.

DR. FREILICH: I just want to add that, on top of that, one of the risk mitigation strategies, considering I think everybody here agrees that these are high risk trials, is intense surveillance.

So, it is not only the inability to get good regulatory type data, but it is the inability to get good data to be sure that you are keeping your patients safe.

DR. SIEGAL: So, let's address the question, since it is already getting quite late.

DR. FLEMING: One final comment, and that is the expanded access or a way of getting this product onto the battlefield where everybody gets the same intervention is relatively uninformative to what you would get if you did a properly controlled trial, particularly due to the nature of effects that are being postulated here.

Reductions in mortality from 58 percent to 50 percent will not be discernible in an uncontrolled trial. While we have heard valid issues of the nature of the challenge, in many areas of clinical research we have found

that it is extraordinarily difficult to do quality research but, if quality research even in those settings where it is extraordinarily difficult is critical to be responsible to people who will be using interventions, to give them informed insight about the use of those interventions, then these are challenges that we have to address.

My concern is precisely for the military, that if we are going to get an answer in an urban setting and that answer isn't, in fact, reasonably reliably predicting benefit to risk in a military setting, then we aren't satisfying our responsibility to those individuals who, in the future, would be offered that intervention without having had proper research.

My sense is, if we have been told, as we have, that there are 1,300 to 2,000 people already who have fallen in this context, it is not a small challenge, but even 500 people randomized as part of a broader experience would provide the potential for very significant enlightenment about the extent to which the results in an urban setting apply to the context of the military.

DR. SIEGAL: I have a question for you, Dr. Fleming. In your view, is the study as designed

constituted with enough statistical power to deal with some of the concerns that you have expressed?

DR. FLEMING: It is properly powered, think, for what effect sizes we have been told that the team is expecting to be able to detect.

It is powered for a difference of basically 58 percent reduced to 49.4 percent. This is properly powered. I have already mentioned, statistical significance here is going to be obtained at 58 versus 52.4.

So, I would argue it is very adequately powered because you are going to see a difference that is 5.5 percent that is, in fact, statistically significant. In view of what we have been told about the nature of the risks, you do need to see at least that level of survival effect to offset at least what we understood today to be potentially plausible clinically significant adverse events.

My big concern is, a, to what extend do the 115 safety data truly reliably give us insight about what to expect in RESUS.

B, what fraction of these people in RESUS will truly be in that category where it matters what they

receive, so that we can actually benefit them. C, is this result adequately generalizable to the context of how this product will be needed if it is shown to be effective.

Now is the time. We can't put that off three years. We can't come back in three years and say, okay, RESUS is well underway. It is now giving us a result in one setting. We surely wish we understood in a broader context what benefit to risk is, but we didn't design the trial in an adequately generalizable way. Those are the three types of concerns that I would have.

DR. SIEGAL: Let's try and address question one. We have been talking about safety signals and adverse events. First, do we actually believe that we can extrapolate from an orthopedics trial to a clinical trial such as is proposed, any better than we can extrapolate from the pig data? Is there a consensus on that question? So, we really can't make any judgements at that level. Okay.

DR. FLEMING: To me, it is not always quite that simple. What you are willing to say is 115 is no more relevant to RESUS than animal data is to RESUS?

DR. SIEGAL: Probably not as good.

DR. QUINN: The question right now is, are 115 adverse events directly relevant to the planned RESUS study, yes or no. We should at least first state that fact.

Are the patients that are going to be seen out in the field similar to the orthopedic individuals that were enrolled in 115, in the other surgical cases.

I would posit that they are different. I can't really extrapolate. To me, it is apples and oranges right now because it is a different -- it is saying, are the results of the study of 115 generalizable to a much broader context out in the urban emergency setting. To me, I didn't think they were.

DR. FLEMING: Just to follow the logic of the team in 1995, that was talking about what was it called, a hierarchical way forward, and that strategy was to start in a low risk setting and, if things are fine, then go into a higher risk setting.

That logic makes sense. The only way that it falls apart is, what if it is not find in a low risk setting. Then where do you go in terms of the high risk setting. That is roughly where we are.

To argue that it would have been relevant to have

seen a pristine safety profile, and that would have been relevant, but when it is not a pristine safety profile it is completely irrelevant, to me, I struggle with that.

I can understand. I am struggling with, is it fully relevant, but I would be equally perplexed to argue it is completely irrelevant.

DR. HAUSER: I wasn't here in 1995. I have got no dog in that fight. It just doesn't make sense to compare those things. They are apples and oranges.

DR. QUIROLO: I agree. I think that the orthopedic study was using this product as a blood substitute. Some of these patients didn't get the product for days after their surgery, and it is irrelevant in the surgical setting because they were already recovered from surgery and someone just decided that they were anemic and they gave them this product, and probably they could have fluid overloaded them. I don't know the details of all of that.

This is a completely different study. Nothing I have heard is relevant to this, to giving this as a bridge before you get a transfusion. There is nothing here.

I don't believe the animal studies are relevant.

These are anesthetized animals. They were given drugs. It tell you that, yes, this can resuscitate people. It delivers oxygen. Beyond that, I don't think it tells me anything.

I think that what this company needs to do is something like a phase II trial with some kind of consent to figure out whether the SEAs and whatever they had problems in the orthopedic study is relevant to trauma. There is no trauma study. It really needs to be done. We can't just sit around here and chat about it.

DR. SILVERMAN: May I comment on again, the FDA draft guidance document suggests a hierarchical approach. You start in a setting where you have very few expected adverse events, so that you see a signal.

If you have an adequate profile in that setting that allows you to move forward into this other setting having some reasonable assurance that, against red blood cells, you are okay.

The reason that we are here is that it did not show a safe and adequate safety profile in that setting. So, you don't know where you are. There has been no adequate safety demonstrated in any clinical trial.

DR. QUIROLO: The orthopedic trial was not this kind of a trial. It was using this product as a blood substitute.

This trial is not a blood substitute trial. The patients in that trial got the product sometimes days afterward because somebody thought they were too anemic to go home or whatever.

I don't think that the logic to me -- I am just a pediatrician, so what do I know -- but the logic to me is that nothing that I have heard makes me think that it is relevant to trauma.

DR. EPSTEIN: We understand that issue and that argument. What we are struggling with is the standard for a trial with waiver from informed consent.

It sets a higher bar. I will just read. To minimize harms, the risks associated with the study are reasonable in relation to all available information about the medical condition of the subjects of the study, the risks and benefits of standard therapy, if any, and the risks and benefits of the proposed intervention or activity.

So, the question here is, where does the burden

lie. In the absence of safety data can you satisfy the conditions for waiver from informed consent, or must you affirmatively have enough safety data to believe that you can waive informed consent.

I think what you are hearing from the FDA that it is the absence of an affirmative demonstration of a reasonably safe product that concerns us.

Why? Given that there is a different clinical situation in a medically stable orthopedic surgery patient, nevertheless, what we have and what really no one has disputed is an excess of safety signals.

So, the available data base from human studies is telling us that there is an excess of safety signals. In essence, the entire counter-argument has been about conjectures of subsets, namely that you have hypotension in a younger person, absence of co-morbidities, they are already hypovolemic.

These are all conjectures about the idea that the product might be safer in that setting, but we don't know that.

We don't know that the baseline morbidity in someone in hypovolemic shock is not predisposing toward an

even greater risk than was seen in the stable patient.

It is the absence of affirmative findings of safety that leads us to think that we are not satisfying the condition of waiver form informed consent. That is the crux of the issue. Where does the burden lie?

DR. PICKERING: With regard to the clinical studies, I had a somewhat different view. As I said earlier, I think what we should be focusing on is death, since that is the end point of the study.

In one of Dr. Silverman's slides I think she said the overall mortality was 3.1 percent in the HBOC groups and 2.1 percent in the control groups. So, there is a small excess of deaths, but I would say very small from what we have seen so far.

When we are looking at the potential for a substantial reduction in deaths from this, I am not overly concerned about the safety.

DR. KATZ: I hate to agree with surgeons. It is just against my genes. As a survivor of traumatic hemorrhagic shock, i would have given consent gladly to this trial, and we could talk about why. It has to do with immunomodulation, perhaps.

At any rate, I was asked to come to a meeting by Biopure several years ago to look at the orthopedic trial. I said, you aren't going to show this to the FDA, I trust. You guys are dead.

Had you done a trauma trial and demonstrated the same side effects, I would have been enthusiastic, but if you think you are going to give this to a bunch of patients with elective orthopedic surgery, you are out of your minds. They ignored me, but that is okay.

So, I look at the safety data. I am apparently 180 degrees off once again. If what I considered serious adverse effects -- death, myocardial infarction, stroke, dialysis -- and I look at that in a trauma trial and assume that it is anywhere in the ball park, then I think the trial should go forward, perhaps restricted to RTSs that are worst prognostic. I haven't figured that one out yet. I am looking at this as a glass half full.

DR. CRYER: I will address it, too, Fred. I think just specifically the question, it would appear to me that the safety profile or adverse event profile, yes, there is some, but when you take it in relation to the fatal adverse event profile of the patient population in the study, that

it makes sense.

I would think that it would fit the waiver of consent the way that I heard you say it. That would be my opinion.

DR. SIEGAL: That is question three. We have to come back to that. Do you have another point?

DR. HAUSER: I was just going to say that I think the bar for an acute care study has to be somewhat different than the bar for a chronic intervention.

I think that the orthopedic trial was a chronic intervention. This is an acute care study, which cannot be reasonably expected to be done without waiver of consent.

Nobody, there is no subset of people who are in hemorrhagic shock who can sign for consent. The average time for an LAR to show up is probably about 12 hours in most places.

So, this is not one that will be able to be done. If we want ever to be able to improve the outcomes of these kinds of patients, we are going to have to make some changes in the way we look at where the bar is drawn and whether there is a proactive need to demonstrate affirmatively using a safety profile using admittedly a bad

study as a predictor.

We need to be in the other camp. What happens to younger people, less than 70, less than 50, wherever you want to draw the line. Do their eyeballs explode? No, they get a little hypertensive. So what?

The reality is we need to be able to do trials like this and we need to be able to do them with waiver and in appropriate patients. Otherwise, we will never go anywhere. We will never improve ever the outcome of hemorrhagic shock or any other acute care event that occurs either in trauma or anywhere in medicine.

DR. FLEMING: but you agree that we are not talking about the issue being solely that they get a little bit hypertensive. That is not the issue.

DR. HAUSER: That is not an issue. It is a non-issue. It is a complete non-issue. If the hypertension is driving the AEs that you are looking at, I haven't drilled down. When you drill down, if that is what is it, those are not AEs. They are just not.

DR. FLEMING: So, is there no bar in your mind about an intervention, maybe not this one, but an intervention that induces significant increases in

debilitating strokes and MIs, in dialysis, in cardiac arrest, et cetera, you would say the same thing?

DR. HAUSER: I am sorry, would you repeat that?

DR. FLEMING: Your answer seemed to suggest that the safety issues are really of very tertiary importance and you characterize them as, if somebody becomes hypertensive, this is something I can deal with.

I don't think we would be here today is that was the only issue. At least my understanding of why we are here -- and Tom, it is interesting to hear your thoughts, too, because I think we spent many years on cardiorenal together where death clearly is number one, and that is something that I strongly endorse as well.

There are major irreversible morbidities and other very significant events that occur in a cardiovascular domain and other cerebral vascular domains, et cetera, that also play out significantly.

I have heard many patients argue that a serious stroke is as bad as death. So, what I am probing on is not to disagree with you if this were just a matter of having patients become hypertensive. It is much more than that, that I am struggling with.

DR. HAUSER: As I said before, I think absent a very small subset of patients, for instance, with cervical fractures who are at risk for craniovascular injuries, I think that stroke is almost unheard of in this patient population, certainly as a function of their hemodynamic presentation.

It is basically unheard of and it would not be something which would drive my considerations for safety in this setting.

Sure, stroke, I don't want to have a stroke, nobody wants to have a stroke, but I don't think in this setting it is a reasonable end point, and I would ask some of the other trauma surgeons here if that is their perception.

DR. BUCHMAN: I concur with Carl. The problem that I sense I am having communicating to the committee is the frequency with which the significant adverse events occur simply as a consequence of the best care we can provide today.

Patients in this category will often develop significant renal insufficiency requiring dialysis either as a consequence of their injury or quite possibly as a

consequence of the current aggressive resuscitative approaches we use.

The relevance of the orthopedic data done essentially in an elective context in well tuned, but otherwise often chronically ill patients with a variety of the cardiac and vascular and pulmonary diseases that go along with old age is not directly applicable to this patient population.

The question I am wrestling with, which is something I think has been raised around the table and also by our colleagues at the FDA, can I imagine a phase II study, some kind of an intermediate step, which will really inform the decisions about the structure of the present trial.

The problem is, as Gil mentioned, there is no such thing as informed consent, either from the patient who is in shock, or from the legally authorized representative who doesn't show up for four, six, eight, twelve hours, that is going to tell us, will this product, infused right away, actually make a difference in the outcome of these deathly ill patients.

Without aggressive intervention, all these people

die. With the current intervention, somewhere around half the people die.

So, if there is a potentially useful new therapy that has some adverse effects but has the potential to reduce the mortality even by an absolute value of seven, eight, 10 percent, that becomes an extraordinarily powerful opportunity for the trauma community.

Now, I would put it to my colleagues, both in basic sciences as well as in the trauma bay with me, can you envision any intermediate trial that would actually inform this type of waiver of informed consent trial? I personally have struggled with this. I can't.

DR. PICKERING: I would just like to comment about the hypertension issue, which we have heard a lot about and I guess is the reason why I am here.

Obviously, hypertension is a very emoted word and it is being called the silent killer and all of that, but looking at the data that we have seen today, I have to say i am very unimpressed.

Most of it is just a number. We saw one slide of the number of patients who had a blood pressure systolic pressure over 200 recorded.

Many of these were probably elderly and may have been having blood pressure similar at rest. When you do a stress test in a patient who you think or know has heart disease, you possibly will stop the stress test when the systolic pressure reaches 220, but that is sort of rather arbitrary.

We were told about two cases of malignant hypertension out of the 1,400 patients or something like that, and one patient in whom the increase in blood pressure appeared to coincide or precede the onset of a stroke or MI, which was a patient in the coronary angioplasty trial who I think had been on nitrates and probably had a lot of cerebral vascular and cardiovascular disease already. So, I would disregard that patient.

In the South African trial of 80 patients, we were shown a pretty flat blood pressure profile as a result of changes during multiple transfusion. Personally, I don't think this is a major concern.

In table 3.B that Dr. Fleming referred to in the surgery studies stratified by age, there were three strokes in the HBOC group and zero strokes in the control group. I think most of us wouldn't make too much of that in terms of

statistical significance.

DR, FLEMING: Tom, you are looking at the less than 70 group only?

DR. PICKERING: Yes.

DR. FLEMING: The total data are ten against one.

DR. PICKERING: Yes, but if those people are being excluded from the trial --

DR. FLEMING: Now you are relying on a subgroup analysis. Most cardiorenal folks are pretty cognizant of how treacherous that is. You are willing to ignore the seven against one?

DR. PICKERING: Well, I don't think it is interpretable one way or the other. So, I am not impressed.

DR. FLEMING: If we would recognize for a moment tat, at best, that subgroup analyses by age and just looked at the totality of the data you would say 10 against one.

What I am hearing from my colleagues is, stroke should be incredibly rare, but it isn't on HBOC. Now, I am not willing to conclude that this is proof of a given level of excess, but 10 against one at least gets my attention.

DR. CRYER: Let me address what Carl said. These patients do have myocardial infarction and they do have

strokes. It is not the usual kind of stroke that you would think of as a stroke like am embolic one, but it is usually a diffuse brain ischemia as a result of prolonged period of low flow.

In fact, it could be that -- you know, the data from this study would be extremely hard to interpret. If you get me five new patients to the hospital who would have normally died before they got here and now I have got to operate on them, I am not going to have the greatest results operating on those patients, probably.

Let's say I save a couple. Could those patients have a higher incidence of those ischemic events? Yes, they potentially could. Whether it is the fault of the drug or the patient's disease, that you finally got me a patient so sick I have never had the opportunity to take care of one before, there is going to be some difficulty in interpreting what the event is.

DR. FLEMING: That is, of course, exactly right. That is why we have a control arm and the control arm backs up what people are saying. It is really rate, and it is. It is one, but in the HBOC it is ten.

DR. HAUSER: I would be interested in the three

in the less than 70 group, whether those all sorted out to being people who were either in the 50 to 70 group with underlying cardiovascular disease and/or people with craniocerebral injuries who were at risk because of injury to their cranial vessels, which is a completely separate issue.

DR. KLEIN: I guess I am still struggling with the lack of phase II data in this setting. Even if we say that the orthopedic trial isn't relevant, in point of fact, virtually every compound similar to this and this has shown increases in stroke and myocardial infarctions in a variety of settings.

The only trauma trial was stopped earlier. Different drug, different model, excess mortality, which no one expected.

So, I guess in trying to figure out whether we are seeing a safety signal here or not, I need a bit more data. I need some phase II data before I feel very comfortable.

In fact, the drug may be a problem. We are assuming that the small number of severe adverse events are going to be overcome by the potential benefit, but I see

very little in this setting to really tell me that that is a reasonable thing to expect.

DR. FREILICH: We struggled with trying to figure out, is there a way that we could do this with consent, exactly what you are discussing, a phase II trial with consent.

We would not have spent this time -- and we spent hours deliberating about much of this with our research advisory board.

The FDA did make a recommendation in the 1990s, as Dr. Silverman stated, that there is a sequential pattern. It is logical in most studies that you do a controlled phase II in a very controlled environment, et cetera, et cetera, and eventually go out of hospital.

That is not always necessarily logical. What you end up with is, you lose the rational risk benefit ratio because you are using it in a control environment where there is little benefit, because they have blood.

So, you have the same risk. It is kind of like giving -- I am an ID doc. So, I have to come back to ampyterosine(?), I am sorry.

Let's say you want to give ampyterosine and

compare it with an astatine(?) swish and swallow for thrush. Now, of course you are going to have a lot of adverse events because it is not any better than the one you already had available.

So, if there is no good way to get consent in a capacity where you maximize benefit, you are just left with risk, and that is really what happened.

You know, there is a little bit, finally, of proof in the pudding. Most of the HBOC companies actually have gone out of business.

The reason, in my mind, is exactly this, that the approach, it appears conservative and careful and cautious but, in fact, it ignores the requirement of high benefit in order to put it all together.

The final point is that there are only two companies left with advanced tech HBOCs. There are some in the beginning of clinical trial development.

It is interesting that both Biopure and Northfield came to the realization that the way to get a pivotal trial and eventually a biological license application is to give up this blood substitute option.

In the United States blood is relatively safe and

available, and go where blood is not available. If someone can figure out a good way to do a phase II trial with consent where blood is not available, then I think that would be fantastic.

DR. CRYER: I think this, rather than an ampyterosine trial, is much more akin to a chemotherapy trial, where the mortality is going to be high, the chance that the drug has worked is relatively low, and the consequences of taking the drug are high.

I mean, there is really only one fundamental difference between a phase II trial in that and a phase II trial in this and that is the consent issue. That is it.

There is no way to get the phase Ii data in this particular disease with a truly informed consent. I would even argue that there isn't a way to do it in chemotherapy either because you hit the patient up with a last ditch effort to live. It is analogous.

I think that I couldn't agree with you more, that there should be phase II data and then we analyze it somehow, but how do we get it if we don't do a trial.

DR. KLEIN: I appreciate the problem. I think the analogy to chemotherapy is one that I find a little bit

disturbing because the patient dies or the patient gets better.

Here, Sergeant Wright survived. I would have hated to have given him something on the battlefield that killed him. That is the issue I have without having a little bit more data and it is difficult for me.

DR. FINNEGAN: As the token orthopedic studies, all orthopedic studies are totally relevant, but in this particular case, this study bears no relevance to what we want to look for.

As Dr. Hauser said, these are normotensive, totally toned, multiple other disease process patients, which is what you do total joints on.

I do think we can do a phase II study. Maybe it is going to take a little creativity and a little give and take on the part of both the sponsor and the FDA.

I think if you take the people who would qualify as the RTS one and two, which is the people who are going to be either dead on the field or dying as you go, and you could come up with some very specific guidelines as far as blood pressure, pulse rate and respiratory rate, that possibly that could qualify as waiver of consent.

A phase II study might be able to give us with say -- I don't know what the numbers would be. It might be able to give us some data we could look at.

I think the other reason that is needed is, if you look at the third part here, I drilled through the data I could and I could not see any safety data for the higher doses and the rate of administration that they are postulating. I think that would also push for another phase II.

DR. SIEGAL: So, is there anyone who wants to talk at all about vasoactivity?

DR. CRYER: There is no question that this is a vasoactive drug.

DR. SIEGAL: Yes, I think we would agree. Then let's move on to question two, please, discuss whether the available preclinical and clinical data are sufficient to estimate a treatment benefit for all cause mortality in 28 days in the proposed RESUS trial.

DR. FLEMING: The third sentence we did just pass right by. Is there consensus? My understanding is that the FDA's concern about limited safety data for this higher rate of administration hasn't been contested. There is

limited data. It is roughly 10-fold and we don't have data on that.

DR. SIEGAL: It was just addressed, which is why I thought we could pass by it, unless somebody else wants to come back to it. So, do you want to talk about question two, reminding ourselves that we are going to have to vote on question three and this is relevant to that.

DR. CRYER: I will start with no. I mean, again, a phase II would give us a lot more information than we have now if we could figure out how to do it.

I don't think you can just take animal data and figure that out. I think there are a couple of things that you would have to do.

One, even the animal models really don't specifically follow this design. That could be one more thing that wouldn't be that hard to do, but you would have to start with unanesthetized animals, give them the drug, anesthetize them. It would be a difficult experiment.

Then, I don't know how to get -- it faces the same problems we talked about earlier, in terms of not knowing exactly what is going to happen to that control group.

DR. BALLOW: I find that it is harder to get studies through the animal IRB than it is sometimes through the human IRB.

So, you are always going to have that variability and that leap from preclinical or animal studies to the clinical arena. It is just unfortunate, but that is the way it is.

DR. CRYER: There are places that are doing it. If you would accept sheep, for instance, the burn guys in Galveston have a huge sheep ICU that is all done in awake animals.

They get local anesthesia and so forth and they get woken up, but they are set up to do ICU studies and could potentially do something like this. I am sure others could, too.

DR. BUCHMAN: I think the question is, is there an animal trial that you can conceive of, a preclinical trial, and/or a clinical trial, that is really going to inform the treatment benefit question.

We have heard around the table that animal studies don't really inform what we might expect for the desperately ill, seriously injured patient.

Is there a clinical trial that you could imagine that would at least provide information about the potential benefit of a rhesus trial short of the rhesus trial itself?

DR. CRYER: The only one that comes to mind to me would be ruptured abdominal aortic aneurysm. Again, that is an acute setting and, while they are awake, I don't know about informed consent being truly obtainable. You could by a family member, certainly.

DR. BUCHMAN: I think it would be very difficult to get informed consent because they are brought to a medical center and they are told, gee, this is where you have to be to save your life. Incidentally, do you want to sign up for a trial. I mean, it sounds coercive on its surface.

DR. CRYER: And you have blood available.

DR. HAUSER: I would like to agree with Gil, that I don't think the currently available preclinical data are sufficient.

I think that there are data, however, in the animal models to suggest that, or actually to demonstrate that the HBOC can sustain life in the absence of cells.

That being the case, I think that there are going

to be situations and scenarios where there is going to be better data in the human arena than others.

I think that the longer the transport is, the more likely in certain kinds of bleeding where, for instance, it is progressive rather than abrupt, and that is why I don't necessarily like the gunshot scenario, but the progressive solid organ hemorrhage in prolonged transport.

So, the splenic bleeder that is taking time to come out of the field, that kind of patient is going to be able to survive to reach care with a circulating hemoglobin solution, and will not without cells.

There are ways to structure studies to increase the number of patients that have these prolonged -- whether they are rural transports like you saw in Louisville, people six hours after the combine injuries coming from wherever. Those things are doable and those could be done. Again, it is very hard to do that without waiver, or impossible. I don't see a way.

DR. SIEGAL: Are you satisfied that the animal studies that have been haven't got a built-in bias in favor of HBOC 201 based on the difference in volumes and so on?

DR. HAUSER: There are multiple biases that were

built into them, multiple. There is a lot of lipstick on that data.

The reality is that it still demonstrates that, under certain circumstances, HBOC will sustain life in the absence of cells. That is what we are dealing with in the prolonged transport circumstance.

DR. FLEMING: To me there are maybe two extremes in addressing this question. One extreme is to ask whether or not the animal data and the collective evidence that we have to date reliably establishes what survival benefits we should be able to fully expect.

Clearly they don't. In fact, if they did, we wouldn't need to do the trial. We would have the answer. That is not a standard that we would expect to meet in decision whether to do a phase III trial.

The other extreme is, do the animal data give us a proof of concept established level of plausibility that justifies embarking on a major full-scale phase III trial, particularly in the setting of non-informed consent.

To me, that is also extreme to think that is the case. Absolutely not. They don't provide that. Do they provide evidence for sufficient plausibility of benefit to

launch into a clinical study?

My sense is yes. That would be typically what we -- we would go from an animal study like this to a phase I trial or aggressively to a phase I phase II trial, and I am very much in the pathway of Keith and Tom and some others that were saying a while ago that what seems logical here is to go to a phase II trial.

Now, we have had a lot of discussion about a phase II trial being difficult to imagine what it would be in the context of waiver of informed consent.

Is there a middle ground. Is there, in fact, however, an alternative where you would do a phase II trial in a setting where there is waiver of informed consent but, rather than saying we are poised here on the basis of animal data to justify launching a phase III full scale, randomized trial, seems incredibly aggressive.

If we can't think of a way to do a phase II trial in a consented population, would a measured step be to do a phase II trial in a population where there is waiver of informed consent.

DR. SIEGAL: That has already been suggested by Dr. Finnegan, I believe, using just simply a higher trauma

score or a lower trauma score.

DR. HAUSER: I would like to explore that, Tom. I think that is a good approach. The question is what the proof of concept is in the animal data.

There is a French proverb, big remedies for big problems. This is a big problem and we don't have a good handle on it.

The question is, is the proof of concept that is established in the animal world, does it justify a jump from a phase I -- and phase Is are done here. I assume phase I was done and it doesn't make people's eyeballs explode.

Does it justify the jump from phase I to phase III with waiver of consent. As a trauma surgeon who deals with these kinds of issues, from my point of view, I am thinking I don't see a way around it, as Ken said.

I would love to see the classic sort of regulatory 101 approach, where you do this first, that second, that third, and you are very conservative.

I am a conservative person also. I like to do cutting edge stuff, but when it comes to my patients, I go very slowly, and I am slow to add new therapies into my

patients.

If I have nothing to offer to somebody, where basically every patient is a compassionate patient, that is what the nature of this trial is. Every patient is a compassionate use.

So, do we have the justification and are we willing to take on the ethical task of creating this as a new pathway for acute care studies.

DR. CRYER: While he is coming to the microphone, one other thing comes to mind to me, and that is, if the animal data is going to be the proof of concept, then what you really need to know is, in the study population that you have chosen, how many of the patients in there are analogous to the animal study that worked.

That would require some effort, and you have to go to the chart and you would really have to get all the data. There are groups out there that have already done this like the GLU grant, the people doing those studies have accumulated a lot of data that you could probably communicate with and then go back and find out what their field criteria were and work it backward.

The idea would be to find out how many people had

a repairable injury that were in profound shock, that had some length of time before they could get blood.

The key there is what you don't know, and you won't know from the NTDB is how many had a repairable injury.

So, if you got four bullet holes to the venacava and two to the heart, you know, you are not going to get that patient through no matter what drug you give them.

If 80 percent of all those people who die have that injury, you are going to have a hard time getting a successful trial.

On the other hand, if 75 percent of them do have a repairable injury, then it is a different story. That would be worth knowing, that information.

DR. HAUSER: I agree with you but, in a stratified trial, those are going to sort out to be the same, hopefully, in both sides, the unrepairable ones.

DR. FREILICH: Two comments. One, Dr. Finnegan, you made a recommendation to consider changing the RTS criteria to a higher mortality trial, and we would love to do that.

The problem is that you end up with a trial that

is scientifically ideal but not doable, or potentially so. The question is, is there a compromise where you can find one.

Right now, with an RTS of one to five, you have so few patients actually such that, in an intermediate, typical medium-sized level trauma center, like the University of Alabama, you can only expect if you got everybody, all EMS systems, the whole city, all the counties, 12 per year.

In a large trauma center, such as shock trauma in Maryland, somewhere between 24 and 36. I am not sure exactly.

What becomes difficult in a prehospital setting where you are not just training a few clinical research coordinators who can enroll occasionally but you can still keep them doing quality work, you have the whole city to train in order to currently enroll 12 patients.

If you go down, for example, to one to three, you will lose about a third of those and you are down to about eight a year.

It just becomes very difficult. I am not saying it can't be done. I am just saying that I think that the

committee should know that.

The second point I wanted to make is that the RESUS trial actually is designed, although it is an exception from an informed consent trial, as a phase II-B-3 trial design.

Now, you could break it up artificially and say, after two, stop, reevaluate, submit your data to the FDA formally. That is the former, somewhat old fashioned, frequentist approach.

FDA has actually proposed that we consider adaptive trial designs baysian methods, which are really somewhat of the avant garde of how you do studies.

From the point of view of safety they are no different. What they are, at the end of your interim analysis, you look at the same safety data, but you don't waste those 50 patients and then go back and start all over again.

There are statistical methods to do this and FDA certainly could work with us. I am just saying that artificially breaking it up at a phase II-B and then a III doesn't necessarily gain you very much in terms of the safety of the patients.

DR. FINNEGAN: I am not sure I would interfere with the avant garde part of the research, but I do think that if you took all of the major trauma centers in the country -- and you may be more comfortable with certain ones than you are with others, but I think if you talked -- the group I belong to is the Orthopedic Trauma Association, but if you talk to any of the trauma associations, they could probably come up with certainly 50 or 60 bodies, that would then give you -- you really don't -- I mean, if this bombs and somebody comes back and says, where is your safety data, the answer is, we didn't have any.

So, you do need that intermittent step. That is why I am talking about being creative. Maybe the creativity is -- I don't want you to lose the 50 or 60 patients, but to do it in a way that you do look at the people who are going to die.

If you do something on somebody who is going to die and they die, that is fine. If they live, you are a hero. If you do something on somebody who probably would have lived and they die, then we have a problem.

DR. FLEMING: Just to respond to this, the concept of adaptive designs of baysian methods is a smoke

screen here.

This isn't going to substantively alter what our challenges are. My understanding is that what this committee has been willing to accept is that we have animal data that, in some sense, is informative, but it is highly uncertain as to the degree of its reliability.

Certainly it didn't accurately predict what we saw in 115. We had to do 115 to get the understanding. Now, that might be, along with another 700 people, information in kind of a phase I-II context, except what I am hearing from the committee is, those 1,400 people, including 115, are minimally relevant to the context of this RESUS trial.

Therefore, my understanding from this logic is we have got the animal data and, as I understand, in general, in clinical development, that basically enlightens whether we go on to phase I, aggressively whether we go on to phase I-II.

Almost unprecedented, whether we would jump to phase III, when we are in fact stating that the data that we have and the 1,400 people already in the clinic from this product isn't relevant to the context of the RESUS

trial.

Therefore, the comment that I was making is, aggressively it would be to say, we do want to move forward here.

We want to move forward with a phase I or aggressively a phase II trial. In my view, that would be a study that is separate from the phase III because I want everybody to have access to this data.

If you do this as the intermediate analysis in a phase III, only the monitoring committee gets access, and this is something that everybody -- the FDA, the patient community, the military, the investigators, the advisory committee, everybody needs to have access to those data.

It is a separate stepping stone trial that would facilitate our judgement about whether to do phase III and, if so, how and, in fact, it doesn't play an irrelevant role in the regulatory process. It becomes a second trial.

One issue that has not been discussed at all today is what strength of evidence do you need to approve an agent, and we are talking two sided 05. That is pretty weak evidence statistically, but if you had a phase II, phase II-B screening trial that answered the question, is

it in fact now truly plausible that a phase III trial would be positive and how to optimally design that, we are in a far better position to move forward to that phase III.

So, I was suggesting that the intermediate step would be a phase II trial and, if we can't think of a way to do it in an informed consent setting, it would be in a setting with waiver of informed consent, because that would be a much more measured step than jumping into the entire phase III trial. That is essentially, at least, what I was putting forward as what could be justified by the data.

DR. CRYER: I certainly couldn't argue with that logic.

DR. QUIROLO: How many patients do you think you would need to have to do what you are saying in this phase II?

DR. FLEMINg: My sense is the phase III, which is what I call SOE-I trial, strength of evidence of one study, because it is only targeting a two sided 05, is in fact properly powered with roughly 1,150 people.

The phase II screening trial that would be basically looking at these same end points in a screening fashion would have 300 to 500 people.

If, in fact, that study was giving -- it is a screening trial. So, if it screens in an intervention on survival and safety, then it would lead to the conduct of a confirmatory trial that now actually could be somewhat smaller in size.

So, it is still a substantial step because you are talking about randomizing, but you are talking about randomizing several hundred people instead of well over 1,000.

DR. QUIROLO: I don't understand why that trial couldn't be rolled over into the next trial.

DR. FLEMING: Because if, in fact, you want to include data in a phase III rolled over trial, the data monitoring committee is the only body that gets access to that information.

It is a phase II-III. I always say, if you do a phase II-III, write the check for phase III. FDA has to sign off on the phase III. They are not getting the data at the end of that phase, nor are the investigators. No one else is getting it.

It is in fact simply the data monitoring committee and now you are putting on the data monitoring

committee a drug development responsibility which wasn't, in fact, the intention in the concept of data monitoring committees.

Now we are getting into the problems around adaptive methods that sound terrific in terms of flexibility, but they are taking away from the people that need to be in the drug development roles those people that need to be reviewing the data at the end of that phase.

Therefore, we are only asking the FDA and the scientific community to buy into this measured next step. At the end of that step, everybody gets access to those data to make an informed judgement about whether you should go on to phase III and, if so, how to do it and, in fact, to write the informed consent.

Those are two separate complementary trials. One, the screening trial, is a supportive trial in a two trial package. The other is the full registration, fully powered phase III.

DR. SIEGAL: Does a phase II like that satisfy the waiver requirements any better than a 10,000 subject study would?

DR. FLEMING: That is a very valid question. It

is still a challenge to answer whether we have sufficient basis to make that judgement.

To my way of thinking, there is a middle ground between not moving on and moving on to the full scale phase III trial.

If there were a way to do this phase II study in a consented population where the answers are relevant to the context of the RESUS trial, I would surely favor that.

I am suggesting that, if there isn't, then there is a middle ground here between randomizing 1,150 people and not moving on at all.

DR. EPSTEIN: I would like to follow this line of thought with perhaps a question back to you, Dr. Fleming, which is what patient group do you envision in the trial.

It seems to me that there are two sort of polar opposite approaches, one of which is a consented trial in patients at low mortality risk, or certainly lowest mortality risk in trauma.

We don't particularly expect to see benefit but where you might be able to study safety. The drawback in that trial is would people get consent.

In other words, if they are at low risk and you

are counseling them, you are probably going to do okay, you might need blood, are you willing to be randomized.

DR. FLEMING: The drawback in that trial from the way you have characterized it is, it doesn't give me a screening assessment of efficacy.

DR. EPSTEIN: That is correct. That is my key point.

DR. FLEMING: That is of concern to me.

DR. EPSTEIN: That is my point, is that at the one pole you can see a consented trial in a lower risk cohort, where you could get safety data in comparison to standard of care, but where you have essentially nil expectations to show efficacy.

The other pole is a waived trial, waiver from informed consent but, in that setting, it would seem that we are closer to the model that Dr. Hauser put forward where he asserted, well, every patient is really a compassionate use subject.

Why? Because what is being envisioned there is very high mortality risk. I mean, why do we allow compassionate use exemptions? We allow it when there is no feasible alternative.

You heard an example, the young lady who had Evans syndrome and needed to buy time for therapy to work. So, I think that generally we would agree that if you had a very high mortality cohort, you could envision, based on proof of principle in the animal studies, going forward with a reasonably small trial where you are looking for efficacy.

I think that the caveat that we heard is, well, you have got to be pretty careful how you select these people because, if you are looking at penetrating trauma, there may be just unsurvivable injury. You know, that 80 percent may not budge.

Then you get into, I think, the two difficult questions which is, how high does the mortality risk need to be in that cohort, and how are you going to select those patients so that it is not unduly confounded when there is no possibility of benefit.

So, I think what I am putting forward here is that FDA is willing to consider designs of phase II studies either consented or unconsented, but the devil is in the details about what is the population group that you are going to study and what is the expectation for the output

of that study. Is it a study designed to look at safety or is it a study designed to look at efficacy.

DR. FLEMING: I don't know that we have ample time to give this complicated set of issues its full due. You are raising very key issues.

The principle that I would put forward is that, if you do this screening trial, it should be done in the context that will enlighten both the efficacy and safety issues that we need to better understand in deciding whether to do RESUS and how best to do it.

I grant that there are different variations to how that could be done that might, in fact, be more satisfactory from an ethical perspective and scientific, but I would urge that it be done in a way that enables you to get enlightenment on both efficacy and safety sufficiently close to the context of what the RESUS trial is proposing to do, although I have already said that I am a little concerned that the way RESUS is currently configured is itself not adequately generalizable to a context such as rural settings and military.

DR. CRYER: I will just comment that, as Tim said before and I raised before, being able to measure safety in

this population, the AEs, how you are going to assess them to the disease versus the drug, is so complicated and so complex because there are going to be so many of them, that it is just going to overwhelm -- what do you do if you have 100 patients and 500 AEs. That is what you are going to have for all the survivors, and I guess the deaths by definition are AEs.

DR. FLEMING: You are absolutely right. That is why the randomized control is imperative and that is why the link to the oncology setting heard earlier is relevant.

That is what we have all the time in oncology. Yet the randomized comparison does enable us to sort out what is disease related that is frequent from what is added by treatment.

DR. HAUSER: Let me think further outside the box here. Is it possible to do both of these in a two track fashion?

Why would it not be possible to do something which was in a more controlled setting which was looking at safety while, at the same time, basically going forward at the same time on the same track, basically a compassionate use trial in patients who were close to death from

hemorrhagic shock with perhaps prolonged transport, and perhaps to have the same DSMB looking at both sets of data at the same time, and then trying to draw conclusions as to efficacy from the compassionate use and safety.

DR. FLEMING: Therein lies the problem, drawing the efficacy from compassionate use in the context that has been laid out before us.

That would work if we thought we were going to take a situation where we would have 70 percent mortality and reduce it to 20 or maybe 30.

If we are going to reduce mortality from 58 percent to 52, or 58 to 50, neither of those sources of information will enlighten the efficacy issue.

DR. HAUSER: I wouldn't shoot for that. I think that we are talking about situations where you are going to have zero survivors versus you are going to get maybe 20 percent or something like that. We would have to pick these people such that long distance transports, people who are going to die.

DR. FLEMING: That sounds a bit reminiscent of oncology trials that, in phase one, look at a pre-terminal cancer patient that often can be very insensitive to a true

effective therapy.

We may not be giving this agent its best chance if we are trying to find out in a population, where everybody is going to die, can it rescue somebody.

DR. HAUSER: All we can do, I think, is do our best to design the trial so it is likely to show efficacy. I think at that point we can look at the animal data and we can look at people who will have consistent bleeding and bleed out to a hematocrit of zero. We can try to pick them, try to find ways to do it, do our best.

DR. CRYER: There is also an HBOC in phase III trials, in trauma patients now. How did they get the appropriate data that made it okay to do that trial?

DR. KATZ: No, the trial has finished accrual and we are waiting for the data. It is the other elephant in the room.

DR. CRYER: So, what did they do to get approval to do it. What were their initial studies?

DR. EPSTEIN: The long and the short of it is for the competitor product, there was a phase II trauma study in the ER in consented patients.

Then that was compared to a retrospectively

designed historic control. That was phase II. We did feel that there were sufficient findings of apparent safety and efficacy to warrant a phase III study.

In other words, we didn't conclude that safety and efficacy were proven by a study of that design, but we certainly felt that the data were compelling and did provide the rationale for going on to phase III in a randomized, prospective controlled trial.

DR. SIEGAL: And that is waived informed consent?

DR. EPSTEIN: Oh, yes, that is field trauma with significant hemorrhage and waiver from informed consent, yes.

DR. SIEGAL: Anyone else want to talk about question two for now? Then let's please try and go to question three, since it is already quarter after 6:00. After considering all available data, do the potential benefits outweigh the potential risks for individual subjects in the RESUS trial. This is the one question that we need to vote on. So, discussion?

DR. BALLOW: I am not a trauma surgeon but it seems to me, if you either take the RTS or you take the blood pressure with the pulse, we are really talking about

risk benefit ratios in doing this study.

It depends on how you move that signal, either RTS or blood pressure. If you move it too far to the left and the RTS is like one or two, you are not going to get any safety data at all, because those patients are really at death's door. That is what you said; correct?

If you move it too far to the right, then you may not see an impact on the benefit as far as mortality goes. So, you are really caught between the devil and a hard place. It is really a difficult decision. That is why it is really critical to try to choose -- I am sure the people who put this protocol together struggle with the same issue, where do you set that line.

You know, for me it really comes down to risk benefit ratio. We have heard so much discussion about this, is it really 58 percent or is it something less.

Those are some of the areas that I am struggling with because we heard so many different opinions from the sponsor, from the FDA, what the actual risk of these patients is for mortality.

I would feel much more comfortable if I really understood that it was somewhere in the 50s or even if it

was in the 40s, 45. I think I would feel comfortable to go with this study.

DR. HAUSER: Just to address that, although the numbers that are put up are sort of the 58 numbers, and I don't really believe them, I do believe they are someplace in the 35, 40 percent range.

I think that in good level one trauma centers we bring that down a little bit, and certainly with short urban transports we bring it down a little bit, but I think the numbers are still high and they are still very high and this is a very badly injured group of patients that have a very significant chance of dying, although I don't buy the numbers that have been put up. Any of the other trauma surgeons here want to --

DR. CRYER: Yes, I would concur with that. It is probably in that neighborhood, of the numbers that Demetriades put up, in an urban center.

You have got to remember that Los Angeles County now, we have 20 minute catchment areas and 13 trauma centers in our trauma system. So, we don't have somebody who doesn't get to us within 20 or 25 minutes.

So, given that caveat, I think that mortality is

going to be in that 35, 40 percent range in penetrating and maybe even lower in blunt.

DR. HAUSER: Let me go on in that point. I think that the rapid exsanguination in penetrating trauma will serve the same function in the short distance inner city transports that the longer distance transports in the rural blunt trauma scenario will serve, and that they will each sort of equalize out because it is sort of the area under the curve for hypotension or for shock times time that leads to the mortality. That will drive it in both scenarios.

DR. CRYER: Those numbers can be actually obtained, the real numbers. If you take the sites you have selected and ask them to pull their patients that meet the criteria for the last year and do a little work, you can figure out exactly what it is.

DR. FLEMING: Just with this enlightenment that we have heard, if it is true that the mortality rate in the control arm is closer to the 30, 35 percent range, either they are going to have to presume a bigger relative risk reduction if they want to keep their sample size at 1,130 or they are going to have to proportionately increase that

sample size considerably, just as an aside.

DR. DUTTON: I generated a fair amount of that data from our trauma registry looking back over the past five years in current practice.

It is based on prehospital vital signs. So, these are prehospital calculations of the RTS. That is exactly where this 58 number came from.

I believe it is the best data we can generate to know what the prospective risk in this population is. What it includes, the reason it is higher when you look at the NTDB, rather, the mortality is lower in the NTDB is, you have already passed the survival test. You have already lived long enough to get to the trauma center.

DR. SIEGAL: Can you give us some sense of the heterogeneity?

DR. CRYER: Do your patients include all of the people who had a scene, that didn't make it to the trauma center, in other words?

DR. DUTTON: Once they start transporting, they make it to the trauma center.

DR. CRYER: So, it is not the DOAs.

DR. DUTTON: What is included is a number of

patients who had an RTS greater than one at the scene who arrived with an RTS of zero, pumping on their chests. That is what is eliminated when you look at the NTDB.

That is why the difference is. We went and got this data specifically, using the prehospital vital signs in the best way we could.

DR. CRYER: That also would have been eliminated in Dr. Demetriades' data. Our LA registry would not include the DOAs.

DR. HAUSER: The other thing is that the LA County data probably has a considerably higher penetrating trauma population than does.

DR. FINNEGAN: I would like to suggest that the answer to this is exactly what he said, which is that it depends entirely on where they draw the line in the scale.

If it is closer to the left, then the benefits are going to definitely outweigh the risks, but you may not get as much information. If it is closer to the right, then the risks are going to outweigh the benefits. So, it depends entirely on how you design it.

DR. EPSTEIN: I just want to reiterate a point that you heard earlier from FDA, but to make sure that this

point is clear in people's minds when they approach voting on this.

This is the heterogeneity of the subject population. Why does that concern us? Let's say for the moment that 58 percent expected mortality is valid and, you know, there is reasonable data that has been presented to the agency.

The problem is that you have got this 42 percent that were going to live. They are going to get exposed to the potential toxicities of the HBOC.

Now, in each individual patient with that same 58 percent risk of mortality you might argue that doesn't matter. The problem is that the underlying group is quite heterogeneous.

With the revised trauma scores ranging from one to less than five, you have a very wide range of expected survival in that cohort.

What concerns the FDA is that, absent a stronger safety profile, we are uncomfortable exposing the patients who are the higher survival end of that cohort, and we are not convinced that that then meets the trial standard for 50.24, waiver of informed consent, which is the probable

benefit to individual subjects.

It is the issue of whether the individual subject is the average study entry subject or is, in fact, a member of a heterogeneous group.

So, part of what concerns the FDA is not just the 58 percent, but the underlying heterogeneity of expected mortality in the study subjects under the design.

DR. KATZ: Well, it was the question that I asked Dr. Silverman earlier, if the entire group was homogeneous and 58 percent, would we be here. The answer was maybe not, is what I heard.

So, moving the line to the left seems to be what would make you comfortable. I guess my interest is, is that 50 for the whole group or 51 or 40-something?

DR. CRYER: There is no way of knowing. You don't know whether a patient -- until you know what the actual injuries were and whether they were repairable, you won't know whether or not a patient was going to survive without the drug or not, or even had the potential to survive without the drug or not.

DR. KATZ: I understand that, but whether it is RTS or some other set of vitals that have been validated --

DR. CRYER: But it is validated in large populations. It is not validated on individual patients.

DR. KATZ: I understand that, but if I know I have got a group with an RTS of 4.9, if I have got 100 people that are supposed to be in this trial and their mortality rate is only 30 percent, I don't think I want those people in the trial, or 20 percent. I don't remember the number.

If I know that the expected mortality in 100 patients with a trauma score of X is 47 percent, have they passed my threshold? That is what I am asking and I think that is what FDA is asking us, in a certain sense, as well.

DR. SZYMANSKI: I was wondering, would it be possible just to analyze each trauma group separately, control and treatment of the trauma score. Would that help in terms of heterogeneity or would 1,000 cases be too few to have the separate groups?

DR. SIEGAL: Is somebody prepared to answer that question? Could you restate the question?

DR. SZYMANSKI: I was thinking that if you are just taking the different trauma scores and have the control and have a treatment group and analyzed them

separately, so you would get some data that would be valuable.

DR. FLEMING: Yes, you can and ideally, in fact, that would be a wonderful situation to be in, where you could look very broadly at a wide range of severity and understand what treatment effect is in the individual groups.

That, however, is going to require an amount of information that is going to well exceed what we could practically achieve.

So, what we do instead is enroll a population that is appropriately inclusive to allow adequate generalizability and then do some sort of exploratory analyses as to whether treatment effect differs in the group.

The problem that we are in right now is actually even somewhat different from that. My understanding is, is there globally or in certain types of populations now already in hand sufficient data on plausibility to indicate that potential benefits are likely to exceed potential risks, to justify going forward with a trial that would be randomization in the absence of informed consent in any of

these groups.

That is essentially the question that I guess would mean, to follow your thought, do we have some good data -- ideally phase I, II data or phase III data from related products, that would enlighten us as best possible about what is that cohort that is most likely to have favorable benefit to risk.

My concern after the day today is that it doesn't sound like we do. We have preclinical animal data and we have data from 1,400 people randomized to 201, but where the committee is pretty concerned about the relevance of that data.

DR. CRYER: I think that, on balance, that the answer to this question is -- well, I think the only data we have on outcomes is in the animals, that is analogous to the patients that are in the trial.

If you are going to say the only way we can go to the next step is to extrapolate that data as a plausible potential benefit to the patient, then all the patients in the trial would potentially benefit, except for the ones who had lethal injuries, and you don't know who they are until after you tried to operate on them.

I think that the answer to that is, yes, the level of severity of the stuff that is going to happen to these patients, even the ones that are kind of on the right-hand side of the bell shaped curve, are so high that they overwhelm at least the patient safety issues that we had.

If the animal data in any way could be extrapolated to those patients, then yes, I think the answer to this question is probably yes.

DR. SIEGAL: Is there any more discussion? Are we ready to vote? Since we seem to be ready to vote, let's do so. Maybe it would be best to poll the individual members of the committee starting with Dr. Ballow. May I remind you that you may abstain?

DR. BALLOW: Dr. Ballow?

DR. BALLOW: I am in favor of the study with close working relationships between the sponsor and the FDA to really try to choose what the appropriate cut point is and perhaps tighten up this issue about homogeneity or heterogeneous population.

I am a little less clear what the FDA means by that because there are so many variables in trauma. I think

they can probably come to some kind of a compromise to push this study forward.

I think it is very difficult to do a phase II trial. It still has to be unconsented. Even if you did the trial in the emergency room or in the trauma bay, you still couldn't get consent on those patients, and then you change the whole scope of the study by initiating the study in the trauma bay.

I don't see what else is left other than to go forward with what is proposed but to try to increase the risk benefit ratio, to try to maximize that risk benefit ratio and try to address some of the homogeneity issues, which is one of the concerns by the FDA.

DR. FLEMING: Is it too late just to add a comment to this?

DR. SIEGAL: No.

DR. FLEMING: I guess one thing that is on the table here that really came to light and I was almost going to say it before your comment is, we are trying to decide whether to go forward, but we are also trying to decide whether to go forward with RESUS.

What is complicating this is the added need to be

able to justify going forward when we can't get informed consent.

Part of the difficulty here is that, if animal data -- let's suppose we could get everybody's consent. If animal data were essentially what we say we have -- and in almost any setting I am aware of that would justify not going forward to a full scale phase III, but to a phase I-II, then why is it when we add the informed consent issue to is, we actually would go to phase III. Do you follow the logic of what I am trying to say?

Even if the informed consent issue wasn't on the table, if we are saying the available data from 115, the available clinical data, isn't relevant to this setting, therefore we only have the animal data, even in a setting where we can get consent, generally we don't say animal data justifies the conduct of a full powered phase III. We would go to some measured next step.

I am having difficulty understanding how, when you add to that, that we aren't going to be able to get informed consent, that you could actually jump to the phase III trial on animal data.

DR. FREILICH: I just actually wanted to back up

what Dr. Fleming is saying, actually. To some extent that is correct, but I am not sure what you gain by doing a phase II separately.

It would be an enormous victory for the sponsor, to be honest, to get a recommendation for a phase II. That would be just fine. I am just not sure what we have gotten out of it.

To say that, in an adaptive design, you cannot submit the data to the FDA, and really the analysis -- I mean, one could have a simple agreement. There is no continuation of enrollment after the first 50 patients, whatever it is, just like any other old frequentist method.

I am just saying that in an interim analysis only the DMC makes the decision. One could certainly think out of the box from that point of view, at least in my view.

The analysis could be just as comprehensive that the FDA would do if it was a phase II going to the III. Either one, I think, would be actually a victory for the sponsor, actually.

DR. FLEMING: For clarity here the proposal, at least from one of us, isn't an adaptive design. Forget informed consent. It isn't going from preclinical data to a

phase III or a phase II-III or an adapted design.

The point is that the normal stepping stone from preclinical data is to take a measured step of phase I or, aggressively, phase II.

The proposal on the table, at least for me was not to do an adapted design. It was to do a phase II trial and everybody gets access to it when it is done. It is a traditional phase II trial.

That would be a screening trial. It is not 50 people. It is more on the order of a few hundred people that would give you the direct insights about safety and efficacy.

The only issue that I wanted to probe here on is, if informed consent wasn't on the table and we are saying, all we have is preclinical data, doesn't that normally lead us to do a phase II? If that is the answer why would we, in the absence of informed consent, jump to phase III.

DR. CRYER: I would like to acknowledge what Dr. Fleming said. What I had in mind really was that I believe that this is a true statement for the phase II part of the trial.

I agree. I have said over and over again, we

won't know -- and the company very well may want to change the trial design after the phase II part of this particular trial because there are so many unknowns here Let me just qualify what I said, that I agree with this.

DR. SIEGAL: could I just try to clarify something? Question three is not to vote on the RESUS trial, as I understand it, and maybe Dr. Epstein can clarify this. It is simply how do we feel about the available data and the potential risks and potential benefits.

DR. EPSTEIN: We are not asking the committee to do FDA's work but we are asking for advice, whether this expert group feels that the probable benefits outweigh the potential risks.

This question is in the context of the RESUS trial as it has been proposed. I think what we are hearing is that there is a varying level of discomfort about the trial with its current design and some level of support for something intermediary.

That would be a modified design, you know, people are talking about phase II. That is really a different question. That is question five.

I think what FDA needs here is a clear sentiment about the trial as currently proposed. That is the issue on the table at the moment.

We have this trial on hold. We are looking for your scientific judgement about the underlying question, which is whether the potential benefits outweigh the potential risk.

That is for the current trial as has been discussed here, as has been proposed, as is presented in the briefing materials for the committee.

I think that if we get a clean answer where the committee stands on that, we can then move much more easily to the question of potential redesign or potential phase II trial.

What we are getting is sentiments in favor of going forward but under a different model. That is not this question. So, I think we do need a clean answer on this question.

DR. HAUSER: A question, again for the FDA, whether this is, for the purposes of 21 CFR, whether what we are talking about here is whether our sense is that the risk benefit ratio makes us want to look for something with

a waiver of consent. Is that what you are looking for?

DR. EPSTEIN: Yes, because the trial as proposed requires waiver from informed consent.

DR. HAUSER: And then to go on from there to deal with the other issues.

DR. EPSTEIN: Yes. Now, there may be other trials that could be done under consent and only have to meet the standard of 312 for a routine IND.

This trial, by its nature, hemorrhagic shock, would require meeting the standard 50.24, this specific design, this specific trial.

Again, just for the sake of the committee, I will just reread what Dr. Silverman showed you when she described the criteria under 312 and 50.24.

If we come in a later stage in the discussion to talking about a consented trial, the standard is that research subjects are not exposed to unreasonable risk.

However, in the context of 50.24, which is the criteria for waiver, it is a higher standard. It requires not only minimization of harms, which I read earlier, the risks associated with the study are reasonable in relation to all available information about the medical condition of

the subject, risks and benefits of standard therapy, if any, and risks and benefits of the proposed intervention or activity.

Additionally, participation in the research must hold out the prospect of direct benefit to the subjects in the study. That is a higher standard.

So, you would be answering a different question later if you say, well, we can contemplate a consented trial in a different cohort. That would be a different question. It would be on the 312 standard.

This question is about the RESUS trial as described to you earlier today and in the briefing material, which is a trial under waiver from informed consent.

DR. KATZ: So, Jay, we are supposed to make our decision based on exactly as they -- can we not anticipate soe give and take between the agency and the sponsors in light of this discussion that would tweak it here and there?

DR. EPSTEIN: Absolutely. I think it is inevitable that we are going to continue speaking with each other. I think we have heard a lot of very useful ideas

which we need to fully consider.

If the committee members have proposals for a modified design, we will hear that in question five. Question three is about the current proposal.

DR. SIEGAL: So, with that clarification, Mark, would you like to revise your comments at all?

DR. BALLOW: No, I think they still stand with the caveats that I mentioned before. It comes down to risk benefit ratio, really.

The nature of the patients we are talking about, I can't really see redesigning or going in a different direction.

DR. SIEGAL: Dr. Cryer?

DR. CRYER: Yes. I think that basically if you take patients that don't have oxygen circulating around and you give it to them, it has got to be good for them.

DR. EDWARDS: Given all we have heard today with all the available data and hearing from the patients that have experienced this as well as from my colleagues around the table, as I look at the potential benefits, I think that, yes, there are more benefits that may outweigh the potential risks, but I, like many of you, also feel that

there are some changes that need to be made, and I will address those in question five.

DR. FINNEGAN: I do not believe that this study can be done without waiver of consent. Therefore, I would answer yes.

DR. KULKARNI: I have problems with all available data because I think there isn't too much available data. I also agree that you can't -- I mean, it is impossible to do this study with consent. So, I would say yes.

DR. MANNO: I would say no. I say no in large part because I haven't seen demonstration from the data presented today of minimization of harm to the potential subjects.

DR. QUINN: I am going to agree with that comment, no, just based on the lack of clinical benefit from any of the previous human studies and the potential risks that may be present.

However, having said that, and then I will go on record as that, I do want to come back to a redesign. I do think there is potential benefit. We just don't have the data to go from the animals directly to a III.

I guess if I was redesigning the study I would be

doing a II-B or a II or some sort of transition from II to III. I guess I am going to have to -- just answering that question, it is a no.

DR. QUIROLO: It is unfortunate that they did the orthopedic trial. The questions that were brought up about the safety of this compound makes me feel like they can't go to the phase III trial without consent. I do think that they can pursue this with the FDA.

MR. JEHN: Is that a yes or a no?

DR. QUIROLO: They shouldn't go on with the phase III trial without consent. That is a no.

MR. JEHN: Dr. Schreiber?

DR. SCHREIBER: I say no. I think that we have had lengthy discussion about the potential benefits and we have concluded that you couldn't tell.

We also had lengthy discussions about the potential risks and we couldn't tell. I just don't think that the available data is there to allow us to pass on this.

Honestly, I do believe from the animal models that there is potential benefit. I sincerely believe that, and I think they took a very conservative approach in

projecting what the benefit is. Again, the risk bothers me a lot.

MR. JEHN: Dr. Szymanski?

DR. SZYMANSKI: When I am reading between the lines, it seems that there would be benefit that outweighs risk, but I am afraid that the benefit has not been documented very clearly. So, I must also say no for the phase III trial.

MR. JEHN: Dr. Whittaker?

DR. WHITTAKER: I would also have to say no. I think that perhaps as a group the benefit would, but there are individual subjects with RTSs at 4.9 that I don't think this would benefit.

MR. JEHN: Dr. Swenson?

DR. SWENSON: My vote is no as well. I think that there are still very important issues here about this very complex blood substitute, and this is not hemoglobin inside a red cell.

Dr. Hintze has alluded to a number of other questions that we just haven't even had time to talk about and at this point my vote is no.

MR. JEHN: Dr. Pickering?

DR. PICKERING: I will vote yes. From what I have heard I would agree that the potential benefits outweigh the potential risks.

MR. JEHN: Dr. Klein?

DR. KLEIN: Regretfully, I don't see enough data for me to say yes to this question. So, I am not sure that is the same as saying no, but it is a no.

MR. JEHN: Dr. Hintze?

DR. HINTZE: I am going to abstain.

MR. JEHN: Okay, Dr. Hauser?

DR. HAUSER: To me, this is a compassionate use trial essentially. I think that the data from the animal models convinced me that there is a potential for benefit. So, as long as it passes the test of more likely to die than not, then I think the answer should be yes.

MR. JEHN: Dr. Fleming?

DR. FLEMING: My reasoning is very similar to what Tom Quinn articulated. We have stated in some considerable depth today that we have animal data that provides some level of proof of concept.

We have 1,400 people that have been randomized that raise significant issues, but we are viewing those

data as not being adequately relevant to the context of this hemorrhagic shock population.

Therefore, I can't justify going from animal data to a phase III trial even if this weren't an informed consent issue, but all the more with the informed consent issue.

So, while I look forward to the future questions where I think there are steps that can be taken, no, I can't justify that these data would justify the conduct of the phase III RESUS study.

MR. JEHN: Dr. Buchman?

DR. BUCHMAN: After considering all the available data, I believe the potential benefits outweigh the potential risks. My vote is affirmative.

MR. JEHN: Ms. Baker?

MS. BAKER: It has been very difficult to make a decision on this. Listening to the higher bar that is raised, the standard for the waiver of informed consent and the potential risks for individual subjects, the heterogeneity, I would have to vote no.

MR. JEHN: The chair, Dr. Siegal?

DR. SIEGAL: I would have to vote no also,

although I do believe that there is a real potential for going forward with a modification of this trial which we can talk about.

MR. JEHN: Dr. Katz, as industry rep, do you have any comments?

DR. KATZ: Were I allowed to vote, the trial as presented, I probably would have voted no. The modifications required to get me to vote yes would not be huge.

They might make it very difficult to do the study in under a large number of years, but I think the standard more likely than not to die is kind of what is in my brain right now and my thoughts are that, if I am convinced that the population is at high risk of mortality, that the data from the orthopedic trial doesn't compel me to think that this is a dangerous drug.

The other things that I would be very interested in knowing is how frequently the data safety monitoring group is going to reconsider stuff.

Most particularly, perhaps more important than anything else is how this concept of community consent would be done, hopefully somewhat differently than what was

done for the other trial that has been recently completed.

MR. JEHN: I have eight aye, 11 no, one abstention.

DR. SIEGAL: Okay, let's proceed to discuss question four. Are there additional data that could help inform an assessment of benefit to risk in the RESUS trial.

DR. CRYER: I think as we talked about before, if you could take this -- get a group of these patients and find out how many of them are likely to fit into the animal model, you know, what the animal model showed a benefit in, that that would help.

It would also give a real good idea of how many -- I do think it is very difficult to sort of say, you know, this patient would have made it or wouldn't have made it if we had this drug, without giving the drug.

If you just take the morbidity and mortality conferences that we always do, if you take one of these patients and you applied our standard regimen to them and they die, we are never going to say that this patient could have potentially been prevented.

So, the only time that you would be able to take the data that is already out there and sort of assign some

risk to it would be if you felt some error was made in our current standard regimen.

The number of patients that we actually do that on is very, very small. So, I don't know. You could try to find out, from data that is out there.

One option would be to collect data prospectively or even retrospectively that met the criteria and see what kinds of injuries they had and try to come to some judgement as to whether this drug would have helped them or not.

Then the other potential thing to do would be what the other company did, and that is take a less risky set of patients and try to talk them into taking the drug for some reason.

As I recall, that had to do with trying to avoid blood transfusion and I think we have sort of already established that blood is probably safer than the drug. So, I don't know. Those are my thoughts on it.

DR. FINNEGAN: I would like to suggest that the answer to question number four is question number five.

DR. FLEMING: Yes, agreed. Can we answer them together? That is exactly right. We can say yes to four or

wait for five or should we just tell. Why don't we handle them together.

DR. SIEGAL: All right, let's do that, then, since that is the consensus of the group.

DR. QUIROLO: What about the South African study? Is that a study that would answer question four? I don't know the details of that, how long that is going to accrue or whether that data is going to be available, but it seems to me that is a phase II trial where they have informed consent for the use of this drug or compound in trauma patients, somewhat like the other trial we were talking about.

DR. SIEGAL: I presume one of the impetuses, if there is such a word, for that trial is the risk of acquiring HIV infection in a blood transfusion in South Africa. Is that the reason?

DR. QUINN: I actually don't think so. I do think the FDA should weigh in on this. What is the availability of the data from the South African trial?

Will they be able to look at it? Will they be able -- can you utilize data from a foreign site that wasn't originally registered as an IND at the FDA? Can it

be used to weigh in on conduct of another trial that is being planned for the United States?

We have heard bits and pieces of the South African trial. Its design we didn't really get much information on. We don't -- I mean, we sort of heard a number and a little bit and I know it is under DSMB, so I don't expect to hear the risk benefit ratios out of it, but I do think that that is the kind of trial that would fit this II-B, or II trial. It is not going to fit Tom's criteria.

DR. FLEMING: It is small. It is 50 people. My understanding is that it is 50 people.

DR. QUINN: I thought it was up to 80 already.

DR. LANDOW: As we understand it from the sponsor, the goal is 50. Approximately 20 have been enrolled so far, 22 maybe.

I just wanted to go over the sequence of the informed consent. According to what I read in the protocol that they sent us, the patient has the first choice. If the patient is not conscious or not able to give consent then the legally authorized representative would be next. If there is no legally authorized representative and the

physician feels it is an emergency situation, the treating physician can make that decision.

I don't know if you call that informed or uninformed, but essentially it is uninformed in a way. It is also in hospital, Dr. Silverman just reminded me of that.

The other thing that I brought out in my talk is that it excludes subjects with traumatic brain injury. That is a big difference between RESUS and this trial.

DR. HAUSER: My understanding of the South African process is that they have sort of an ombudsman in the hospital. It is not the treating physician, but there is sort of a patient rep, ombudsman, ethicist, available in the hospital at all time. I assume that would be used.

DR. FLEMING: Just in terms of numbers here, the RESUS trial, if it were fully conducted, and if it were, in fact, giving us a population with roughly our targeted projected death rate of 58 percent that could be reduced to the low 50s, that is a study that would yield around 600 events.

In contrast, the South African trial will yield 20. I was thinking of a more measured step, as we often do

for phase II-B trials, that are roughly a third to a quarter the size of the full phase III.

I was thinking more on the order of 200 events that would then be sufficient to truly allow us to sort out an intervention that truly provides no benefit versus taking forward one that provides encouraging evidence but not conclusive evidence unless, in this trial of 300 to 500 people, if we truly provide a 10 to 15 percent absolute improvement in survival, then that would be conclusive.

If it is in the range of the sponsor's null of no difference versus alternative of a nine percent absolute, then this trial that would have roughly 200 events would give us considerable enlightenment about the likelihood that this would be positive in a confirmatory follow up trial.

I was envisioning a study that would be a phase II-B screening trial as an intermediate step that would be a much more significant step than just putting 50 people on and getting very minimal amounts of information for insight.

This is aggressive in the sense that this is -- I would advocate this be done. If there is no way to do this

in a consented population that is adequately relevant to RESUS, then I would argue going forward with this intermediate step.

In that sense, I believe there is adequate plausibility and established evidence from the preclinical data to justify that.

I am partly persuaded by the reality that this is very different form the orthopedic setting. This is a setting where people don't have access to blood transfusions.

So, with the nature of the preclinical data in that context, it does seem to me to be appropriate to move forward to this intermediate step of a phase II-B screening trial with all of what I completely agree with that the sponsor said they would put in place, which is timely reporting of efficacy and safety issues to a data monitoring committee, or a data monitoring committee would be in place to carefully monitor what is evolving over the course of that screening trial.

I would also, though, urge that, as best possible, to try to get this -- if we do this screening trial -- to be as generalizable as possible to answer the

question for the populations that really need to have this answer, which certainly includes the population that RESUS is proposing.

If anything, as I have said before, I think RESUS should be even more inclusive. I am not persuaded that the elderly patient should be excluded.

I have concerns about whether it is adequately generalizable to the context, such as a rural setting. I like that idea of the rural setting being included that could, at least, take us a step toward the military setting.

My ideal would be that there would actually be even a component of this that would be in the military setting or a separate component.

I worry about getting an answer that the military needs to have as well, but from a context that is not adequately reliably addressing that.

DR. HAUSER: There are actually settings that one could predict, such as true rural emergency room settings, places in the far reaches of Colorado or Wyoming, where all transports are prolonged. If you get enough of them, you can get enough patients like this. There are ways to do

this.

DR. EDWARDS: On that same point, as I stated before, I wanted to comment on some changes that I think are important for this study going forward.

One thing that very much concerned me as I saw this was that we were talking about an urban setting. The last thing that I would want to see, especially as part of this committee and being from Baltimore, too, is to see that the FDA is being labeled then as unleashing in the urban population an unproven therapy in the blood in a population, of course, as you already know, that is very much suspect of the medical community and clinical research in general.

I would hope that we would do something in terms of giving some form of informed consent, and then also using this trial in other areas, as you have already mentioned, whether it be in a more suburban setting or rural area, rather than only focusing on an urban area. That was my suggestion for a change in the trial.

DR. SZYMANSKI: To clarify, the study as you suggested, would that mean that they would need to have informed consent or without? Do they need to have informed

consent for this phase II trial?

DR. FLEMING: My ideal would be to identify a context where that could be done. If that means that we have to do a trial that isn't adequately relevant to the context of the RESUS study and all of the populations that need the answer to the RESUS study, then no.

I am arguing, then, that in that sense we should endorse doing a trial that would waive informed consent as a screening trial that will give us answers relevant to what the RESUS study eventually wants to address.

DR. PICKERING: Just about the possibility of doing a smaller study, it could be that there is an excess of adverse events in the treatment that are not life threatening but might be enough to prevent the definitive study being done and might miss a modest benefit in terms of reduction of mortality.

If a large study is done, presumably it is going to be very tightly monitored by the DSMB. If there is an adverse effect on safety, this will surely become apparent before the study is completed. So, why do we need the additional study?

DR. FLEMING: When you say the additional study,

be more specific, Tom.

DR. PICKERING: I mean as opposed to going through the definitive study where the outcome is 15 percent reduction in mortality.

DR. FLEMINg: Essentially, if one went forward with a screening trial that was providing more on the order of 200 deaths, that study would be able to screen out ineffective interventions.

It wouldn't give us the power in that trial alone to definitively establish a survival effect if there is on the order of an eight percent improvement, but it would give sufficiently encouraging evidence that, together with the safety profile, if it is as favorable as we would hope, would justify a confirmatory and more conclusive trial.

However, if it turns out that, in truth, you would have a 15 percent absolute improvement in survival, then this study could, in fact, even with a sample size of 400 people or 300 to 500 people, could in fact be conclusive.

Whether you would do a follow up trial would depend on the nature of the results that would come from a screening trial.

A screening trial could either, on the one hand, be sufficiently unfavorable in benefit to risk to identify that no one else should go on, and you have actually addressed this with a much smaller sample size.

The opposite extreme, could provide conclusive evidence if there are effects even larger than the sponsor is postulating in RESUS.

If it is in the middle, if it is in the range of that true benefit that is eight percent with a good safety profile, it is a trial that has some chance of being conclusively positive, but a considerable chance also of providing the evidence needed to decide exactly how you are going to proceed in a phase III confirmatory trial.

DR. KLEIN: At the risk of saying something truly outrageous, as we have heard earlier, there has been just concluded a very large trauma trial, different design than RESUS, different drug but it is an HBOC.

I would hope that, if there are lessons to be learned from that trial, which is currently in analysis, that somehow they could be shared with the trial that, again, would be going forward without informed consent and would have some impact on the US public.

I know that is an issue of confidentiality but, nevertheless, it seems that that trial went forward based on lessons learned from an earlier trauma trial which was a disaster.

DR. FINNEGAN: I would like to follow up on that. I think this presents the FDA with a phenomenal opportunity. I do think, as someone brought up earlier, that acute care medicine does not have a good path with which to follow studies.

Lots of times off label use of drugs or equipment or whatever is how we advance the process and certainly acute care is going to be a real part of our world for the foreseeable future.

You might try and come up with a different pathway or this might be one of the ways to learn a different pathway for this kind of problem.

DR. HAUSER: Sine it was me that said that, let me point out that I think in most of research in acute care the low hanging fruit is gone.

We are not going to be able -- the problems that we are going to have to address going forward in the future in order to advance acute care are going to become more and

more difficult and they are going to be in patients who are less and less capable of consent.

So, if indeed the FDA does wish for this process to proceed, I think that this is an important stimulus or this conference should be a stimulus for the development of methodologies such as the ones that Dr. Pickering, for instance, has suggested, for how to go forward in jumping some of these hurdles, not making the hurdles lower, but making them appropriate to the disease process.

DR. SIEGAL: Is there any more discussion? If not, perhaps we should adjourn. I think that we should thank everyone for their incredible input which I hope will have been helpful to the FDA. Do you want to make a comment? Of course. Jesse?

JESSE: I just wanted to second your comment and thank everybody, including navy and Biopure and especially the committee.

These are very hard issues. I think as you know there are many uncertainties and we will take your input with the tremendous importance that it has. I thank everybody for contributing to this.

[Whereupon, at 5:05 p.m., the meeting was

adjourned.]