got the right category. But that doesn't mean it's approvable. It simply means you've got to weigh the risks and benefits in the context of this trial and make a decision whether it's approvable. But it's basically okay to work within the context of prospect of direct benefit.

And then I would follow up that question to ask, this sort of describes a whole series of interventions that would mimic an effective vaccine approach, sort of picking up on I think Ben's earlier comment. If you were simply doing a single dose in order to look at physiologic or immunologic response to that, would we still be working within prospect of direct benefit? And I'm suspecting not in that context, that you'd have to think about a different categorical consideration.

DR. JOFFE: I think that's probably right.

So the answer to your first

question, Jeff, is yes. I do feel like this is the right category to be working within.

The answer to the second question -- if I could again go back to the phase 0 analogy -- so these are trials of new agents where doses that are much smaller than those are expected to be used for clinical purposes are given in the adult setting, maybe even to healthy volunteers, for purposes of looking at pharmacokinetics, and maybe looking at effects on pharmacodynamic endpoints. And often it'll be single drug or a single dose of the drug or a very small number of doses.

And so certainly there, the trials are designed such that it's completely implausible that there might be any benefit to the person. Imagine if it's a healthy volunteer who doesn't have cancer who's volunteering to be a test subject for a new anti-neoplastic drug. There's just no possibility. So clearly then, we would have to be thinking about other justifications in a

pediatric setting -- other categories.

And so if that analogy works here, then I think that the sort of equivalent of phase 0 testing of a new vaccine could not plausibly be considered under 50.52. But testing of a full regimen I believe could be considered.

Again, that's not to say that it would satisfy all the criteria. But at least that could be considered under this category.

DR. FOST: Let me try to sum up the conversation so far. And this is intended as a target. And again, we're not here to vote or make an action item. But it sounds to me like there seems to be some sort of coalescence around the following.

That as a general matter, drugs need to be studied in children -- and adolescents are included in that group -- for scientific reasons, behavioral reasons, and so on. How big or how small those groupings need to be will depend on the facts of the case.

Since Skip gave us a real hypothetical with some meat on it, we've been commenting on it. And it sounds to me like for this hypothetical, there have been several reasons not to include adolescents at this time.

Number one, as Alan said, it's a proof-of-concept, and if and when the concept works, then there's plenty of time to test it in adolescents. Number two, as Alex started the discussion, although it would fit into 52, the facts are the matter are such that the prospects of benefit in relation to the risks are so low at this point that it would be inappropriate to include non-consenting patients or subjects at this point. And I should have said that first, which is the third principle that Len said. As a default position, we should generally not include children in studies unless there's some good reason to do it, or unless it's ready to do it. In general, we prefer consenting

subjects.

So on the facts that Skip gave us, it sounds like so far people think this is not ready for adolescent populations. Is that accurate?

Well, that makes very hypothetical the rest of Skip's question, such as which adolescent -- if we were to do it in adolescents which we wouldn't want to do -- which adolescent populations would we do it in. So maybe we need to tweak the hypothetical a little bit and say what if the first cohort of adults on whom this was done, the concept would look plausible. So it now looked like maybe we should move this along and test it in adolescents.

So is this appropriate? Yes, go ahead.

DR. NELSON: No, that's fine. I'll just point out, historically I started writing this case before the results of the Step Trial were available. So I think that has made the

case more hypothetical than it was originally intended to be.

But I will also point out that based on my reading of the scientific literature, I also chose a hypothetical product that was not the product tested in that trial. So I think it's still -- as I said -- it's still an important issue that will come up at some point in the future. And I think extending the discussion to consider what would be the issues around when you would choose to do that, even if that's not now, I think would be very helpful.

DR. FOST: So let's -- yes?

DR. KON: I apologize because I think this may be a little bit off target.

But I have a question that I've been struggling with as I've been sitting here thinking about this, which is this question of whether in fact if we were enrolling adolescents if they'd be providing informed consent, or if we'd be asking parents for

informed permission since we're talking about an HIV vaccine that is to prevent a sexually-transmitted disease. Therefore in clinical practice, this would be something that potentially adolescents would be able to consent for themselves without parental knowledge. So many would argue that therefore in a research situation, adolescents could provide informed consent without parental knowledge.

And I ask only because I think that, that raises some other issues. And I do appreciate that this is not exactly what we're discussing, but it's a little bit hard for me to think about some of these issues regarding this trial without having a better sense of if we're really talking about parental permission versus adolescents' informed consent.

DR. FOST: Yes, it'll be on the table. But I think you're a little ahead. I think there's an intermediate thing before we get there. So we'll definitely get to it.

Len?

MR. GLANTZ: Yes. In terms of your list of consensus, I think it's pretty good.

I just want to depart from it a little bit though by saying that a question that I had asked is if we find out that this is safe and effective in adults, is there a scientific basis to do research on late adolescents, or can we just clearly extrapolate from that group.

DR. JOFFE: I'm going to tweak the hypothetical now and say that the first round of testing has been done in adults and there's encouraging results -- whatever the goal of the proof-of-concept was, it looked promising -- so that now there's some more plausible reason to think that adolescents may want to participate in this.

So let's discuss it with that standpoint. So we're there now where it fits into 52. Now the facts are a little bit more favorable. One question is, Len's asking

still whether there's any reason -- any scientific reason -- to do it in adolescents at all. But a second reason is if so, which adolescents? Which population? Where are we going to find them? Presumably we're not going to do this in Idaho. So where? And who? And where should this be studied?

MR. GLANTZ: Yes. Just forget about what I said before. For the purposes of this conversation, I think we should forget about the scientific necessity which we discussed, and just go on to the hypothetical.

DR. FOST: Okay. So let's assume some reasonable basis for adolescents. Where should we find them? Skip?

DR. NELSON: Well, I'd also be interested in hearing you unpack promising. In other words, how promising does promising need to be to meet the prospect of direct benefit?

DR. FOST: Well, to move it along, I think we have to assume something like there

was really a lot of excitement.

DR. NELSON: There's been a lot of excitement in the past for it.

DR. FOST: Yes. I think if we say the results were slightly interesting, I don't think we'll get it. I think if we want to get to the other questions, we have to assume that they're exciting enough that people think it's worth plowing ahead. Unless somebody else wants to comment on --

DR. CVETKOVICH: Well, it does help to -- particularly in this field -- you probably know what you mean by exciting and you would have maybe a different opinion.

So the question is we don't have an immune correlate of protection so that you can't assess an immunologic response that will predict benefit let's say, but it prevented all HIV infections in the adult study. Is that exciting? Is that what you're thinking?

DR. FOST: Does anybody else want to comment on the definition of exciting?

(LAUGHTER.)

DR. FIX: Well, I'll definitely say that's exciting.

(LAUGHTER.)

DR. FIX: But I think in this context, it might be useful to put it in -- not necessarily define it that clearly -- but just say that the results were sufficiently promising to move the product forward in the licensure pathway to phase 3 testing.

DR. FOST: I assume something resembling consensus among experts in the field that what Alan said is correct. I don't know how else you can fine tune it without the facts of each case.

Jeff?

DR. JOFFE: A couple other elements at least to throw out. And I guess I would want to say exciting from an efficacy standpoint, not just from a safety.

And if you got good data out of the adults where you didn't know whether it was

working at all yet but you found that it was a highly safe vaccine, would that be sufficient to move on pediatric or adolescent age group? I guess I'd be at least initially a little reluctant to make that jump. So efficacy.

And then I'd also be willing to think about surrogate markers as opposed to end markers. So you hadn't demonstrated that it actually prevented people from getting sick, but you knew that viral load was associated with disease progression, and you could demonstrate that viral load was down by a vaccine.

From my perspective, that -- if those were in fact the facts -- that I would say excitement could be generated by surrogate markers as opposed to definitive end markers.

DR. FOST: Yes, I assume you were not talking about the politics of this. In all of science, there's enthusiasm that's disproportionate to the facts. And opinion leaders get ahead of the facts. And so, we

need to define excited in some procedural way that reasonably dispassionate people without vested interest and so on have reviewed it and say, yes, there's something promising going on here.

So let's assume that, that's the case -- that there's not dispute that the results of this trial in adults met the objectives and were sufficient to move on. And Len has given us permission to bypass necessity. Let's assume people agree it is important to study adolescents of some age, whatever those boundaries are. Where are we going to find them? General population? U.S.? Africa? Where should this start?

DR. FIX: Okay. I'll step into this one. Actually because it allows me to step in with a non sequitur going back to what we were discussing about 45 minutes ago and sort of some of the regulatory issues and policy issues and how you'd apply something off label. And I think a lot of the

discussion thus far is pretty much being logically centered about what could be done, should be done, is allowable within the context of the U.S., but given this is a U.S. FDA panel. But clearly the burden and the applicability of a successful vaccine would be outside of this country. And that's where the huge share of burden of infection and disease is. And clearly, any study would have to involve those populations.

Certainly there would be efforts to involve high-risk populations within the U.S. And there are challenges in doing that, but certainly a lot of folks engage in that -- some in this room. But it would certainly have to involve populations outside of the U.S.

DR. FOST: Other comments?

So because you want to go where the risk is the highest, and where the access to other kinds of care like anti-retrovirals is the lowest? Is that a relevant factor also --

that they're aren't other options for some of these populations?

DR. FIX: Well, I think that is something to throw into the mix. But I don't think that's a crucial piece. And I think that's thankfully -- although it still remains a huge issue, and nobody anticipates treating ourselves out of the epidemic. It's become less of an issue.

But I don't think it's the crucial issue. That is where the burden of infection disease is, and it's where the most relevant potential benefit is for the populations.

DR. FOST: Okay. Because the potential benefit is higher where the risk is highest, and therefore your concern about adverse effects is lower. Concern about adverse effects would be very high in a low-risk population.

Steve?

DR. JOFFE: So I just want to think about different ways that you could answer

this question, just put sort of a systematic approach to it.

So one is you could say that the right population is the one where the benefit/risk ratio for the enrolled subjects is the most favorable. And presumably, that would lead you to -- the benefits would be greatest in those who are at highest risk of infection. And so that would lead you to a very high-risk population.

The second approach might be to say well, the preferred population when we first move into adolescents is those who are able to provide the most robust consent/assent. And maybe that takes you to a different population.

And then a third possibility is we want our enrolled population to map as closely as possible to our target population for the intervention, if in fact it proves successful and is taken into clinical practice. And that might lead us to a third different approach.

And maybe there are others that people around the table can come up with. But it seems to me like each of those is probably a relevant consideration in deciding which is your population. And maybe one of them is the most relevant and ought to be the driving force.

And again, maybe there are others. But at least we ought to be able to think through those possibilities.

DR. WILFOND: Steve, I thought that was great. I like that distinction. And I'd like to at least weigh in a little bit.

I think your first category where the benefits/risk balance is most favorable would be the one that I would probably think of for that first trial with adolescents, and then from there make further decisions.

DR. FOST: I was going to ask how you would rank those. Certainly the opportunity for consent and assent might be very high in Madison, Wisconsin, but it would

be irrelevant if the risk was so low. So as Ben's suggesting, is risk really the driver of this? The others are sort of nice if you can get them, other things being equal.

DR. JOFFE: That's my first impression. But I guess I'm not ready to sort of come to a final conclusion on it, particularly because I really do care very much that the study population -- maybe if we're talking about the sort of very first small focused study in adolescents. Maybe this is less important. But I do really care very much that we begin to map our sort of study population onto our target population for the intervention if it turns out to be successful.

DR. CVETKOVICH: But those are not -- and they're not mutually exclusive at all. So the sequential approach would be appropriate.

I would be very surprised if there would be a situation though where you would

target any pediatric population working in age downward because they can provide consent. There have to be other important factors there.

DR. FOST: Alex?

DR. KON: Well, I'm not sure. I think that this raises a huge issue. Because if we're talking about that the fundamental difference between someone who's 18 -- I'll use that age because I live in California and that's our age of consent -- so 18 versus 17.9 years of age -- is this ability to provide consent versus relying on permission. Then if we're talking about the first in adolescents, if we can move into a group that could reasonably provide consent for themselves, in many ways that can rise very high in my opinion. Because what we're really talking about at that point is people agreeing to something for themselves.

So even if the risk/benefit ratio is less favorable than in a very high risk

group, the fact that these are individuals who can really understand what they're agreeing to and are agreeing to do it for themselves, I think can actually be very meaningful, particularly since if we're talking about something where there's a rather significant risk, if we're necessarily going to the people who have the highest risk to begin with then we run into this problem of placing very high risk people at even more risk. And so I think in some respects, for me it rises very high.

DR. FOST: Well, I'm wondering about how high. At the absurd end of this spectrum, you don't -- to take the famous example that was -- you don't do a parachute study just because you have informed the participants. A study can be just wrong to do regardless of whether people fully understand it or not.

So to give a vaccine that has some risks to a population of children that has only remote chance of ever acquiring HIV in

their lifetime, the fact that they understood it perfectly, you'd say there's something wrong with them if they're saying yes to it.

DR. KON: Yes. I think there's no question about that.

But then if we're talking about for example where are we going to start this, there's certainly places and populations of children who are at higher levels of risk than others but who are still in a situation where they may be able to make reasonable choices for themselves as opposed to perhaps the highest risk groups that might not be able to. Again, we're talking about whether we're talking in the U.S. versus in Africa, et cetera. I think it becomes a real balancing question.

And yes, I would agree that you wouldn't want to do it in a group that has virtually no risk merely because they can really understand it. But at the same time it might make a lot of sense to start with a

group that has a reasonable amount of risk and a reasonable amount of ability to understand what they're agreeing to as opposed to a very high risk group that has a much lower chance of really understanding.

DR. FIX: I'll make the comment anyway.

I guess the question I'll come back with is, is this being viewed as the necessity to do some kind of phase 1, 2a study, either separate or nested to establish safety in this group independent of the adult population data? Because certainly if the context is fully an efficacy study, a lower risk population serves no end for this study or advancing this.

DR. FOST: We're coming up on a break. And I just want to make one comment before the break. But Skip, go ahead, and then I'll make mine.

DR. NELSON: Well, I was just going to try and frame a general question out of

this discussion. I think it's very interesting.

So on the table are these three different populations -- one looking at risk/benefit, at risk in the benefit that fits, the other looking at the eventual target population that you might intend for the intervention, the other looking at the -- if you will -- the population that might often be the most robust combination of permission/assent, assent, et cetera.

What would be interesting to me is here people thinking about those populations, but taking it out of this specific instance. Because here it may be that the target population and the at-risk population are in fact the same. However, that's not always going to be the case, that in fact in some product development the at-risk population -- the target population -- might be different. And there may be interventions.

In other words, I guess to the

extent that the at-risk population as Steve had framed that captures -- if you will -- the regulatory language around appropriateness of risk and benefit, et cetera. One question is how far one might stretch that without breaking it, looking at issues of assent and looking at issues of target. As a general question, even if it's not raised concretely in this particular instance, would I think be an interesting discussion.

DR. FOST: Thank you.

I want to make one closing comment, and then a procedural note about the break.

This is an unbelievably trivial comment, but it's a sign of how far we've come that it is now trivial. When the AZT short course trials in Africa were done, we had this furor in the New England Journal of Medicine about if it's unethical to do the study in the U.S., it must be unethical to do it in Africa. So you had the editor and invited editorialists both making that claim.

And we don't talk that way anymore. That is people have said of course you go to where the risk is, and the fact that it would be unethical to do it in Idaho has got nothing to do with the ethics. It's got to do with the facts. The ethical principle is the same, which is risk/benefit ratio and reasonable prospect of benefit in relationship to the risk.

So it's an obvious comment now. Trivial, as I said. But it wasn't then, and it wasn't so long ago. So I think it's a sign of how far we've come that we can talk calmly about starting where the problem is without being accused of being moral entrepreneurs.

And let me caution the panelists as well the guests not to discuss any of these issues during the break. You can discuss the Celtics, the Lakers, Big Brown, Hillary. All that is fair. But we shouldn't be discussing the topic.

So we'll reconvene in at 10:45, in

15 minutes. Thank you.

(Whereupon, the above-entitled matter went off the record at 10:30 a.m. and resumed at 10:48 a.m.)

DR. FOST: Thank you, all.

So when last we met, we seemed to be in agreement that studies should be done in high risk populations. And even though those might be found outside the U.S., that doesn't make it wrong, and it's not using different ethical principles. It's the same ethical principle. It's just the facts that are different. But it's risk/benefit prospects that matter.

So this might be a time to move now onto the question that Alex anticipated a while ago. And then we also want to be sure to cover Skip's question, which include issues of -- I think we've already actually answered your question, Skip, about which markers might be relevant. Or at least for this case, we considered it not central.

But why don't we move to Alex's questions about all the tricky parts of consent and assent and parental permission when we're dealing with a sexually-transmitted disease, and where issues of privacy are more prominent than they would be for let's say an influenza vaccine or a bird flu vaccine?

So who wants to -- Alex, you were revved up on that. Do you want to start by saying something provocative of how you think it should work?

DR. KON: Sure. I'm always good at being provocative, I guess.

So I guess sort of tying this into I think what Steve -- you were talking about just before the break this question of where do we go and which group do we start with. I think that this raises some major issues because I think many people would argue well, in this group based on the way that many people are doing this that in fact these adolescents aren't adolescents for the sake of

the study. They're really adults because if they're providing informed consent, then we obviate all of the ethical issues. And so we might be able to merely enroll them as we would an adult because they're providing informed consent. And I've heard a lot of people say that actually.

And I think that my fear comes in that there are some very good reasons for allowing adolescents to provide informed consent for treatment in that if we didn't do that, many of these adolescents wouldn't obtain treatment because they wouldn't want their parents to know. But it becomes a fundamentally different question when we're asking them to enroll in studies because we're not really asking them to enroll in this study for their own personal benefit. What we're merely saying is looking at a risk/benefit ratio, and that on top of this there are significant risks merely of being in a study that doesn't happen in terms of personal

information and privacy. And so I have some significant fears of that.

And so I think that therein lies sort of some of my questions of how we would look at that in terms of this study, whether we would really look at this people as adults versus children. So that's some of my thinking. And I would just throw that out for discussion.

DR. FOST: So you're suggesting that the argument for excluding parents is weaker here?

DR. KON: Yes. I think it's much weaker. I think when we're talking about enrolling adolescents in this type of a study, I think there are some significant concerns that I think it's important to actually rely still on informed permission of parents and assent of the children rather than moving entirely away and merely having informed consent and not involving parents at all.

DR. FOST: Skip?

DR. NELSON: Norm, to just lay out a few land -- not landmarks; wrong term -- but I guess some facts -- if you will -- that you could take into consideration.

The first point I think all of the vaccine trials that have been done, that have been alluded to, have all been done with both parental consent and adolescent assent. I'm unaware of any vaccine trials that have been done -- the point absent parental permission being involved under any kind of an argument that it was not necessary.

So that point is not necessarily to address your ethical concerns, but to just say from a feasibility standpoint, that has in fact not been necessary.

DR. FOST: But those are not involving sexually-transmitted diseases.

DR. NELSON: I'm talking H -- yes.

DR. FOST: HPV.

DR. NELSON: HPV. Yes. Absolutely.

DR. FOST: Okay.

DR. NELSON: Yes, absolutely.

There are some parents who communicate around these issues with their children. And I think the trials were larger than three.

That's meant to be just a factual statement. We can unpack the ethics. It can be done.

The second point is the point Alex raises is the definition of a child under Subpart D in 21 CFR 50 does refer back to the legal right of that minor to make a decision about the interventions that are contained in the research. So it opens up the question as to whether or not under the jurisdiction of the location where that research is being conducted, that minor -- meaning someone less than 18, or I guess if you're in Nebraska less than 19 -- might not be considered a child for the purpose of the application of Subpart D. Now the implications of that position is you

would not necessarily need parental permission because they have the right to consent.

Second would be, it leaves an open question as to whether the additional protections for children contained under Subpart D would then not be used for them, which raises I think the ethical concern that Alex is raising.

I might point out that actually as a policy matter, that is pretty much up to the local jurisdiction. There is no view at the level of the FDA about how that decision ought to be decided other than decided by the laws of the local jurisdiction. So what's good for California is very different from what's good for Boston. It's very different than what's good for South Africa, et cetera. So and that is a statement of fact. And there are public documents about that position that are available. Just to lay that out so as people are talking about the ethical issues, you understand at least that's the terrain -- if

you will -- from an FDA perspective.

DR. FOST: Ben?

DR. WILFOND: Skip, that was actually very helpful. And your comments remind me of the fact that we ought not to necessarily think of this parent permission as a dichotomous issue. We don't have to get it from anybody, or we have to get it from everybody.

And I think what's really interesting about your comment about jurisdictions is we could imagine circumstances where we say look, all things being equal, when there's intact families we try to get parental permission, but there might be other people who we might want to be enrolling in the study who either may be in foster care, they may be homeless, they may have other circumstances where parental permission is not readily feasible. But depending upon the circumstances, we could think of those as adults.

DR. NELSON: It's an open question. But I would only caution since you threw foster care in there that the issues of wards of the state are an entirely different issue. I'd prefer us not getting into that issue if you don't mind.

DR. FOST: Jeff?

DR. BOTKIN: Yes, let me clarify what the regs say too in this vein.

Now my understanding is that the waiver criteria that can applicable under Subpart D, FDA doesn't accept waiver in general, but does accept circumstances in which adolescents who may not be considered adults but who can receive clinical care in circumstances relevant to the research can be enrolled in research with a waiver of parental consent. That is not what the regs say?

DR. NELSON: the issue of waiver becomes moot. That's the point. And whether or not you need a specific research statute for decision-making, or whether or not you can

apply treatment decision-making statutes to the research setting is a matter of local legal interpretation.

DR. FOST: So your earlier comments made it sound as if there's no need to discuss this because it's no problem getting parents and children to work collaboratively. You can get sufficient recruitments. Obviously when you can get parents and children to both participate and agreeing, it's preferable presumably.

DR. NELSON: I guess what I'm saying as a practical matter, it's not been an issue in vaccine trials. I don't want to imply that taking what I've just said and applying it to other instances requires some thoughts is the case. But as a practical matter in the vaccine trials, it's not been an issue.

DR. FOST: And remind us. They were done where -- the HPV trials? In the U.S.?

DR. NELSON: Well, I think those trials were done in the U.S. Yes.

DR. FOST: So we're talking about Africa? Len?

DR. NELSON: Yes.

MR. GLANTZ: I think that one of the questions that I would raise to this panel is what is the high-risk population? Because the HPV trials didn't involve high-risk populations. The assumption is that every young woman is at risk. And you wanted to vaccinate them before they became sexually active.

But here, I thought I had heard that we should use a population of high-risk kids. And I'm wondering who in America we would think of being high risk, because that might have an impact on going to their parents. So if we think of high-risk children as children who live on the streets, who are homeless children -- not foster care children. But if we're not thinking of them as kids who

go to Newton North High School -- to use Boston-- or Grosse Point High, but something else, who would they be? Who would we look to try this on?

DR. CVETKOVICH: You mean in the U.S.?

Based on the epidemiology, I don't know that there's a population of at-risk either children or adolescents that could be studied in the U.S. right now.

I would think that once -- if there was benefit in a high-risk population, i.e., South Africa, one of these places where your people -- just regular people -- are at high risk, then those data could be bridged to if our goal was to use the vaccine in a low-risk population because we believed that the benefit would be worth it.

So that would be the progression I would think, unless things change.

DR. NELSON: Norm, if I could just expand.

I think one thing to keep in mind here is the kinds of trials we'd be talking about are fairly large. So even if one could imagine in a small population say of homeless youth in New York that in fact might be at risk, that the feasibility of doing a trial in that population given the size -- even independent of the ethical complexity of assent and consent -- would be problematic in that going into populations that are at risk where it's -- I think that's what I'm suggesting is the epidemiology and the ethics actually head in the same direction relative to the feasibility of the trial would be my hypothesis.

But then again, I don't know how many -- we'd have to look at those numbers. But you're talking fairly large trials.

DR. FOST: Therefore Africa?

DR. NELSON: Well, going into at-risk populations that are definable in ways that are different than imagining trying to

collect all of the at-risk, homeless youth within a -- again, I don't know the data. Other people that work in this field may know the data. But that would be my speculation.

DR. FOST: Alan?

DR. FIX: Yes. I think the comment you were making was that you'd be drawing on populations outside the U.S. as well. But there are again groups working on identifying at-risk populations of adolescents in this country and are successfully working with them with other preventive modalities as well. And again, some of them are in this room.

DR. CVETKOVICH: Right. But I don=t know, and it certainly isn't established, that the rate is high enough to even -- of course it depends on what you're studying. But one would assume that efficacy would be demonstrated in a high-risk population, and then bridging would occur from there.

DR. FOST: So if we're talking

about non-U.S. populations, that raises other questions about how much we know about cultural norms in these populations and what's acceptable. So some of the background readings suggested that adolescents are more likely to be on their own there, that parents are less likely to be involved. So it's maybe not so barren in that regard.

But it also opens up the issue of community engagement for doing these trials. When in addition to the usual problems of doing research in third-world countries, you have now sexuality and highly stigmatized disease. I don't know if these are uniquely pediatric issues, but it certainly would seem to raise the threshold for wanting to have community involvement in the places where these trials are going to occur.

Anybody want to comment on the degree to which that's been done for other HIV trials in the third world? Anything about that, Alan?

DR. FIX: Yes. Well, certainly for our trials for any of the sites involved with us, they had community advisory boards which serve as liaison with the community. And there's a lot of outreach to the community, specifically for adolescents. Certainly in South Africa, we have a couple of sites that have really proactively been engaged with the adolescent populations, and have both engaged and engaging adolescents working with them with adolescent populations with a lot of enthusiasm.

DR. FOST: Other comments? You're making it sound as if parental involvement's just not a problem. It sounds too easy.

Does anybody want to suggest it's more of a problem than has been suggested? Len?

MR. GLANTZ: Yes. I think it depends on the population you want to use. So I don't know if we're concluding here -- concluding is probably too strong a word. If

we're saying here that we can't do this in the United States, and if because we don't go to the high-risk population, as though we should do it in the non-high-risk population? And because I think if we're doing it in the high-risk population -- my understanding by the way is that the vaccine is for sexually-transmitted disease as opposed to IV drug users. That might be a different mechanism involved according to the readings.

DR. CVETKOVICH: Well, a couple things.

It depends on when you're saying this, it depends on what this is. Are you talking about demonstrating efficacy in a U.S. population? There are populations in which that could be done. It's unlikely that that would happen in a strictly adolescent population or in the general population in the United States. The risk just is too low. And so, if you wanted to evaluate heterosexual transmission in an at-risk population, it's

unlikely that that will be done in the United States.

However, we would -- or one would want to develop data to support that use if you had an efficacious vaccine, so that then you would do safety, and if you'd identified an immune response that could be evaluated, then those would be done in U.S. populations without the intent of proving efficacy because the numbers just are not there. The epidemiology would not support it.

DR. FOST: Len?

MR. GLANTZ: So you're saying that we would not look at efficacy but look at the safety in the U.S. population of adolescents?

DR. CVETKOVICH: Correct.

MR. GLANTZ: And we could do that in any adolescent group -- not a high-risk group? We would do the research on everyone?

DR. CVETKOVICH: Yes. Definitely. If we've had an efficacious vaccine and we believe that the development path was

appropriate, that we were going to use it in a U.S. population, then I can't think that would assume that we decided it was safe enough, effective enough that we wanted to study its safety in U.S. population of adolescents. Yes. It could be done.

DR. FOST: Skip, and then Alan.

DR. NELSON: Well, I think, Leonard, this is a little bit of what I was getting at about the potential differences between an at-risk population and a target population. Because as you begin to think from both a risk/benefit assessment as you have limited information about the safety of an intervention, the appropriate population would be one that would be at risk so that the risk/benefit would be appropriate within the context of proceeding with that trial.

Now that may then be at an at-risk population, which by the way it's enriched by that at-risk-ness, makes the feasibility of assessing the scientific objective also easier

because you have a higher incidence of what you're trying to prevent. So the sample size is smaller. So there's both ethical risk/benefit issues there and scientific feasibility issues.

Now ultimately as that product -- and I'm talking in general terms -- as one develops a product whether it's a vaccine or any other kind of a product and you get a larger safety profile, it is possible you may then decide to take it into a population that's not known to be at risk as a population, but where people may then begin to assess that the risk/benefit of individual administration is appropriate just as a general population intervention. Whether HIV vaccines will ever get there is at this point highly speculative. But it's not off the table to where one could then go into a less at-risk population once one has more robust safety data from the at-risk population to further define that in a much larger safety

trial. So there's different scientific objectives that might be used, and then different populations that one might use depending upon the stage of development and the evidence that would be in support of it. So I think that's the sort of issue here.

The general principle in my mind is independent of whether it's located in Washington, D.C. -- that population -- versus Boston, versus San Francisco, versus Iowa, versus South Africa. These are general concepts we're talking about. And then you get into just the epidemiology where that happens to be true.

DR. FIX: I just wanted to ask a question, which is, Therese, if I understand correctly, you're saying that we could study risk in the U.S. population, but not efficacy. Is that right? And that we would therefore do the vaccine trials on people for whom it may not be efficacious just to determine if there's risk. I don't know if I understood

you correctly.

DR. CVETKOVICH: Well, the use of the word risk because we look at that both in terms of efficacy and safety. So there's people at high risk for HIV, which we don't really have in the United States in a concentrated way or in the overall population. And then there's risk in terms of safety.

So if you have an efficacious vaccine which was defined in your high-risk population in Africa because they have an adequate rate of infections for us to even be able to assess the difference, and then you decide okay, this is safe enough. We're going to use it in the general population because we think there's a benefit there. Then you could collect safety data or whatever you thought was appropriate in a U.S. population.

DR. FIX: Yes. And just a couple of comments.

I think regarding the inclusion of U.S. adolescents, I think I would make the

statement that not exclusively in the U.S. rather than not in the U.S.

The additional piece comes back to this establishment of safety and say the U.S. population are not necessarily high-risk population actually which is interesting because it comes once again back to the issue of do you want to fold in a phase 1, 2a component into an efficacy study. But I think certainly the particular reg that we're looking at wouldn't apply there because you're no longer dealing with the direct benefit. And that becomes a totally different issue, I think.

And finally, I think some of us are not sanguine about the need for parental permission is not an issue particularly how you define risk for participants coming into the study and the clear disclosure of risk behavior that might serve as an obstacle for some to participate.

DR. FOST: So I'm a little confused

here.

So let's say this hypothetical vaccine now has been shown proof-of-concept in adults which was sufficient to justify going to a high-risk adolescent population in Africa, for example. A trial was done there and showed promising results, and that it showed efficacy. And so it was now ready for a phase 2, 3 trial. And it was a point where it's appropriate to now to try to bring it back to a U.S. population.

How would we think about where to target a U.S. population of adolescents? Would we again just be looking for high-risk, or would we be looking for a general population? Is this a vaccine that we're anticipating is going to be like HPV that's going to be given to everybody, or just the high-risk kids? So how should we be thinking about studying this in U.S. adolescents assuming it's time?

Thoughts on that? Where would we

start once we're bringing it back home? Are we still talking about high-risk? At what point do we go to a general U.S. population? What needs to be true for it to be tried out in a low-risk population, or a general population? Just that it's been safe or how safe?

DR. NELSON: I guess, Norm, I struggle partly because I think as we hypothetically try to move ourselves further and further downstream, we become more and more--the paucity of data is even more fully felt. And so the question is really around the risk/benefit.

There are certainly huge trials of vaccines that are done. Rotaviral vaccines -- 40, 50, 60,000 is really the kind of trial that's performed. What you need to say, you want to go into a certain target population is very different than if you tried to identify say a population that has a 15 percent incidence of HIV AIDS, for example, as at

risk. And then you've done -- I'm not sure what Step was powered at -- say 2000 and 3000. Lower than that? I think whatever it was, but you're talking 2,000 or 3,000 which gives you a smaller safety data set.

So it really comes down to what kind of data you may well have found in the administration of that product to justify then taking again the risk of the administration of that product and balancing that against the prevention within the population at risk. And as the safety data base becomes more robust, the willingness to go into a population that's less at risk becomes greater.

But I guess I'm just not clear in my own mind how much further specification of that balancing one can do in the absence of any concrete data, unless that's what you wanted people to think about. Sorry.

But go ahead.

DR. JOFFE: Steve, did you want to comment?

DR. JOFFE: Steve Joffe. My sense is that this is going to be driven first and foremost by scientific and study design considerations. And then we will have to work out the ethical issues as a second step.

And what I mean is that if there's good proof of efficacy in high-risk populations in other parts of the world where the prevalence or the incidence is much higher, when we come back to the United States, for example, are we going to need to do efficacy studies in the United States, or can we extrapolate efficacy? And so this is a different context of extrapolation.

So that if we can extrapolate efficacy, and we've got something that's got a relatively favorable sort of side effect profile and we think that the risks are reasonably low and there's consideration about doing this on a population-wide sense in nine-year-olds, for example -- to go with the HPV analogy -- then we can think about our target

population being population-wide, and we will not need to target high-risk children or adolescents now for scientific reasons.

On the other hand, again for scientific reasons, if an efficacy study needs to be done, then you need to do it in a setting where the incidence is relatively high. Otherwise, we're going to need a study of tens of thousands of children which is not going to happen.

DR. FOST: Alan?

DR. FIX: Yes. Just on the issue of geography, I think you'd have to presume that you could blend efficacy data in the U.S. in adults with efficacy data outside because of the complication of the clad issue.

DR. FOST: I'm trying to see if there are any points of tension here to get some discussion going.

Alan, were you questioning Skip's optimism about doing this with parental permission in U.S. populations?

DR. FIX: Well, not just U.S. populations. I think it very much depends on how you're enrolling adolescents, what you're stating the risk criteria are, and the individually-specific risk criteria, and divulging that information to adults.

So if you're just drawing from a general population that you know has high enough endemic rates that you're just assuming that this general risk -- whether or not you're assessing for sexual activity -- is one thing, but specifically for getting into other components of risk, then it becomes fairly problematic. But I think even just assessing sexual activity could be a challenge in some populations.

DR. FOST: Other comments on this? We're running out of steam here.

Skip, are there other issues that you would find us helpful to address?

DR. NELSON: Well perhaps, Norm, it might be useful for you to see if you could

tackle a brief summary and see where there's gaps.

I think part of the challenge here is knowing the path forward is going to depend upon how data emerges. Extrapolation of efficacy is very different than necessarily extrapolating safety or dosing -- which in this case is really immunogenicity -- your ability to bridge from one population to another. If you're able to establish immune correlates, great. If you're not, then your ability to then go from one population to another may be problematic.

The issue of assent and permission is very much locally driven. And what's on the ground in South Africa is going to be different with what's on the ground in Boston versus what's on the ground in Texas or California. So I'm not sure how exploring that -- I guess in thinking back to the population question that Alan -- Steve -- I had a high school friend named Alan Joffe, so

I'm going to constantly make that mistake every once in a while -- but Steve raised about these different populations is -- the risk/benefit population, the at-risk and the assessment of benefit -- that language comes right out of 50.52.

I think the challenge -- or one could frame as a question -- is these other populations -- the target population if that's different or the population that could give the most robust assent and permission -- if you will -- from an ethical protection perspective may be different. And I guess the question is to what extent would people try to frame some flexibility around the application of 50.52 in light of those issues. Or is the only context within which you can do that is through the evolution of data that then would support moving from an at-risk to a target population once data emerges? Or would one try to bring an ethical argument absent data to privilege those populations, I guess could

be explored a little bit. I have my own bias. But having raised it, it could be explored a little bit.

DR. FOST: Well, I'll try to summarize it again and see if people have any comments on that.

So it sounds like there's very strong agreement that children are different, adolescents are different. It's hard to define exactly at what point they become different or how big the groupings are. But in general, studies should be done, particularly for sexually-transmitted disease or a vaccine for it should be done in adolescents. Point 1. Or they should be included in studies at some point.

Point 2. With regard to the hypothetical that we discussed given the dismal history of vaccines, some adverse effects, the fact that we were given a hypothetical that said proof-of-concept stage and given the general principle that we

shouldn't use adolescents unless there's some important need to, that waiting for proof-of-concept to be shown in adults first would be sensible in this situation.

Three, that if and when that happens, when you wanted to include adolescents, you'd want to start with a high-risk population for scientific as well as ethical reasons. And given the numbers that would be needed, that would strongly imply a non-U.S. population.

Four, that ideally parents should continue to be involved, and if that can be done consistent with cultural norms, then that's the preferable way to go, which requires assessment of cultural norms in a robust way with community consultant, community engagement, particularly in other countries.

Fifth, if and when studies in another country are promising, then studies need to be done in the U.S. And it's possible

that there may be differences of efficacy. Maybe Steve, I wasn't quite clear as to why you would think efficacy might be different in a U.S. population than Africa. So maybe we could say some more about that. But certainly safety difference, environmental issues, co-morbidities, genetic reactivity and a whole host of reasons. So safety studies would need to be done in a U.S. population.

We didn't get very much beyond that about which U.S. populations, whether it should be targeted with high-risk U.S. populations, or is that not a large enough group in the U.S. to be sufficient, and so would you then just go to a general U.S. population.

And last, I think we didn't discuss it, but I would certainly affirm your implications, Skip, that the facts are always going to drive these discussions. So how all these general principles get applied will depend on the specific facts that we're

dealing with.

Yes?

DR. NELSON: One of the purposes of this discussion is to try and generalize. And maybe it might be worth sort of stepping back from this case and saying and thinking about the discussion and how some of the concepts that have been placed on the table are important and can be sort of framed in general terms of then usefulness in approaching other cases.

If you haven't seen, part of the intent of the cases is that they sort of build, at least the two today and to some extent then tomorrow explores a little bit different direction about prospect of direct benefit. The two ideas, I think that one could identify -- and I'm doing this as much to invite general discussion on those ideas that may or may not be related to this case.

First is this principle of scientific necessity. Extrapolation is just

one -- if you will -- specification of that principle. But it would imply that research involving children always has to have a scientific objective that's pertinent to the children enrolled in that research. You shouldn't enroll children to answer adult questions. That I think articulated and then applied to other cases would have significant implications for the ethics -- if you will -- of pediatric research. And so I think it's worth pondering that more generally independent of its specification in this case. What are the scientific objectives here as opposed to that principle?

The second is around this prospect of direct benefit. If you were charged as the data safety monitoring board of a particular trial to say at what point there's sufficient prospect of direct benefit to either consider it promising or if you're more effectively and not scientifically driven, exciting. To say what is that? Is that a P of .3? If you want

to talk statistical terms, at what point would you say something sufficiently promising to say it's time if you're not going to drive it to a P of .05?

Now I'm not suggesting we have to answer that. But it's certainly different than .5, or whatever P you get. Some statistician would probably tell me what the P you get with chance. I guess somewhere between .05 and whatever you get which is chance, is that what we're looking for to say that there's prospect? So thinking about it in general terms, stepping back from this case, I think in my mind to hear discussion around those two key ideas would be helpful.

DR. FOST: Steve?

DR. JOFFE: So I guess let me raise one issue that I think is related, and then sort of charged to us to generalize.

When I said what I said about prospect of direct benefit being a relatively low bar -- just a low hurdle to get over and

the sort of thing that one could get over based upon animal models for example, I saw a lot of -- puzzlement's not the word -- but people around the table were challenged by that idea. And I recognized it. I stand behind it. I didn't only say it for the purpose of provoking controversy, and yet I recognize that it was a controversial position to take. And I shifted sort of the burden of the decision to the sort of risk versus benefit justification part of the thought.

I suspect there may have been some disagreement around the table about the position I took that wasn't stated. And I don't only mean in this particular case of the HIV vaccine, but more generally the idea that you could base the prospect of direct benefit on pre-clinical models and that at least that hurdle could be crossed based on pre-clinical models.

Is that something that anyone wants to challenge? Or have we reached consensus on

that point?

DR. NELSON: Well, I'll only point out that's the question for the case tomorrow morning. But you'll get back to this question when you tackle that hypothetical case.

MR. GLANTZ: Yes. I don't know if it's a philosophical or just a semantic issue. But the word prospect -- the word that wasn't used that could have been used is possibility. And you're using prospect and possibility in identical ways. And we could ask why the term prospect was used instead of the word possibility.

So I think you've made the point that anything is possible. Don't you have like any evidence at all? And it seems to me, it doesn't even need to based on animal research for example. You could just come up with a theoretical construct of why something might work, and that would be a prospect of direct benefit too.

But I think what you said following

that, I think that the rest of the rule actually helps define the prospect means. So I don't know that it actually ultimately matters what prospect means, because I think it's defined by the rest of the rule.

DR. FOST: Alex?

DR. KON: So following up on that, I think it's key that what we're talking about is really in this category where we're talking about that a greater than minimal risk.

And so I think to begin with, what we need to think about almost by definition is that anything that we would be considering as a prospect of direct benefit, the prospect would at least need to be sufficient to outweigh anything that's more than minimal risk. And so I think that that's where we come into the key.

And I agree. Some of it comes from semantics. And then we talk about well, now we're going to weigh for this particular study, does the prospect of direct benefit

outweigh the potential risks. But the reality is if we're only going to be applying this in a case that is already greater than minimal risk, I think right there the bar's already been set. That if we're going to contemplate it under this definition, it has to at least be more than merely a possibility. There needs to be a real potential because it needs to be enough to weigh against more than minimal risk. And so I think that becomes the crux of the matter.

DR. FOST: Jeff? And then Ben.

DR. BOTKIN: I guess I wouldn't have concern about Steve's low threshold obviously depending on the other facts of the case.

I would say the prospect of direct benefit does have to be the intent of the research. In other words, you have to include provisions within the research protocol to actually evaluate whether benefit or efficacy occurs or not.

And we've certainly seen protocols that the sponsor tries to claim that there might be benefit, but yet there's nothing included in the study that actually measures whether benefit occurs or not. That for me would be a deal killer in this context.

But what are the other factors that would relate to how low a threshold you go? Severity of the disease? How big a problem is it in the kids? And is it a lethal disease or a minor discomfort, et cetera?. And then of course, the level of risk or safety itself, and if the preliminary safety studies show it to be extremely safe, then I would feel pretty comfortable with a fairly low prospect of benefit to allow that to be an approvable protocol.

DR. FOST: I was just going to say exactly the same thing that the risk of the intervention and the seriousness of the disease matter.

If it's a dandruff remedy, it's a

new shampoo that will improve dandruff, I don't think you need much about prospect of direct benefit to say it's okay to see if it works in teenagers. And if it's a minor tweaking of an existing shampoo, I don't think we'd worry much about toxicity. We wouldn't want prior adult studies before saying kids could use it.

So it all ties in with the likely risk of the intervention, the seriousness of the disease, and existing data.

Somebody else had their hand up. Ben?

DR. WILFOND: Well, both your and Jeff's points really get back to what Steve said way in the very beginning was that one of the reasons you could use a low bar for prospect of direct benefit is because you have this second requirement for the benefits as it relates to the risk, which is what you've been saying. So part of your argument is you can have it as low as you want because it's what's

important is that secondary one.

I actually agree with that. But I do want to at least give one other example that would at least -- not support Len -- but support that direction. And Nancy King often talks about when there's a reasonable chance of benefit. And obviously that word reasonable is wiggle worm, but it's meant to be more than just possible. But whether it's for animal studies or other things, it's a reasonable belief that this will actually have some value. And that's different from just possible. It's not the same as the benefits outweigh the risk, but somewhere in between those two.

DR. FOST: Steve?

DR. JOFFE: Actually I just want to follow up on Jeff's point about there must be intent of benefit. Maybe that's a paraphrase of what you said, and maybe it doesn't capture exactly your meaning.

But I actually think one can

separate the discussion of intent of the protocol and what it seeks to measure from asking sort of factual questions about whether there is a prospect of direct benefit. So for example, let's say that we had convincing, compelling data that a vaccine were efficacious in an adult population whether in the United States or elsewhere in the world, and the data were so compelling that all we felt that we needed to next were safety studies in adolescents.

And let's specify further. And from what I've been hearing from those who know about this area that we don't really have surrogate markers that we could use to look for a surrogate for efficacy in the adolescent population, so that we're faced with a choice between simply doing safety studies versus doing full-fledged efficacy studies in adolescents. And the consensus was that those full-fledged efficacy studies were not necessary.

So now all we're going to do is set out to do a safety study to ask questions about if there's anything different about the risk profile. And presumably that would be a small and perhaps even a single-arm study in an adolescent population. And there was no possibility or intent of measuring benefit either as a clinical outcome or a surrogate outcome, and even the logic surrogate -- the logic surrogate being impossible.

I think we could still say in a study like that that there was a prospect of direct benefit even though there was no scientific intent and no measured endpoint that looked at benefit or proxy for benefit in that protocol. So I think it is possible to distinguish the two from each other and ask one question about the intent of the protocol as far as measuring efficacy, measuring benefit, and another question about empirically, is there a prospect of direct benefit, and if so, how likely and how great

is it?

MR. GLANTZ: Did you say what the benefit is in that setting?

DR. FOST: Say it again, Len.

MR. GLANTZ: I just want to know what the benefit is.

DR. FOST: Say it into the mic.

MR. GLANTZ: I'm just curious what the benefit is to the subjects -- to the individual subjects -- in that setting?

DR. JOFFE: So we have compelling evidence in a vaccine that is approaching licensing, at least for an adult population, and we have -- based on what you were saying at the beginning -- very little reason to suspect that the efficacy considerations are going to be different for an adolescent population. But we want to know something about the safety of the vaccine in an adolescent population in order to support licensing in the adolescent population.

The benefit is it's very likely

that it's going to prevent HIV infection, or it's going to reduce the severity of HIV infection if it occurs based upon extrapolation from data in young adults. And that to me is a very real benefit.

DR. BOTKIN: So in that context -- and I think it's an important point -- if the study weren't even looking at efficacy -- you weren't even collecting that data -- which is different than saying you're going to collect the data but you don't expect it to answer the question based on the prevalence of the disease or incidents of new infection within the population. If you weren't even measuring efficacy, would that be an acceptable trial and you were simply looking at safety alone?

I guess I'm attracted to the idea that if you have strong enough evidence of extrapolation of the benefit side that it's okay to evaluate the safety side of the risk/benefit ratio and make that an acceptable trial. But I guess I'd still want to see the

trial include measures of benefit even if you weren't ultimately going to achieve statistical power.

DR. JOFFE: So I'm setting up a sort of stark example where there's no possibility of getting surrogate endpoints because we don't have decent surrogate endpoints for the measurement. And it's a study that's too small and maybe not a controlled study that wouldn't allow you to look at efficacy endpoints.

I suppose one would ask the investigator to collect data on the incidents of HIV infection and the severity of HIV infection amongst any of the adolescents in the study who got infected. But even if one didn't do that, it probably wouldn't change the scientific value of the study. They're very unlikely in my hypothetical study to be very many or maybe even any infections in a relatively small study.

And yet we're now doing a study in

15-, 16-, 17-year-olds, and we know that among 18-, 19-, 20-year-olds, the vaccine prevents infections, or moderates the severity of infections if they occur.

I don't think it would change my calculus of my risk/benefit judgments where those adolescents if the investigator simply said there's no scientific point, there's nothing feasible that we could measure, and there's no scientific point to measuring the things that we can measure because our study is for example too small.

DR. FOST: Yes. I would stream it slightly differently, which is it would be unfortunate if they didn't at least make some effort to see if any cases of HIV broke out in this population. And you might even want to require them to do it.

But even if they didn't do it, or refused to do it, they're still a prospect of benefit, that is they're getting now a vaccine which we think is highly likely to be

effective, even though we're only looking at safety. The kids who are getting it still have a more than reasonable prospect of benefit.

Skip?

DR. NELSON: I guess I was going to ask Jeff to clarify a question that really reflects your answer. But there seems to be two very different prior assumptions of what's known about the two interventions in the cases that you gave.

In the one case, there's nothing known about efficacy. In the other case, it is known to be effective. And so there's very important different prior assumptions in the cases you proposed.

And the question then is whether in the situation where one knows it's efficacious, and then there's additional information that needs to be gleaned around safety independent of the type of product and the situation, if the absence of efficacy

endpoints or data collection necessarily means it can't be prospect of direct benefit, independent of whether it would be a good thing to do because you've put together your trial, you're collecting data. Why not just add another case report form, et cetera?

But that's not a claim that you can't consider it under prospect of direct benefit, which is a much stronger claim.

DR. FOST: I wanted to go back to Skip's invitation to talk about necessity and to -- maybe I said this enough already, but I want to say it a little bit more strongly -- I think the necessity argument is overrated.

We haveB-so on the one hand I can recite dozens and dozens of examples of drugs that turned out to be very bad for kids because they were just used off label, and they turned out to be bad. So I'm well aware of that.

But on the other hand, 80 percent of pediatrics is about off-label use. And I

don't any of us wants to say that's wrong. We should stop using those drugs, because that's the end of pediatrics as we know it.

So when we give a new antibiotic to somebody with otitis and it's not been tested in 16 to 18-year-olds, or 12 to 16-year-olds, or 8 to 11-year-olds, I don't think it's a tragedy. That is there are other ways of finding out about safety and efficacy of drugs besides prospect of phase 3 trials. And we should have a better epidemiologic monitoring system. And as we get more electronic medical records, maybe we'll be able to do that more effectively.

So the fact that we don't know for sure whether a new drug that's worked great in adults and works great in adolescents, that doesn't prove it works well in three to eight-year-olds, or even one to two-year-olds. That doesn't follow to me that it still should be prohibitive, we should be prohibited from using it, or that we should mandate.

Necessity is just way too strong a term.

Skip?

DR. NELSON: With all due respect, Norm, I would suggest that that might be a misstatement about what I was intending around scientific necessity, which is that should one decide to do a research project that in fact the question you are asking ought to be scientifically necessary. It begs the question about whether or not you need to do that research relative to off-label use. And I think that's a much more complicated question.

So I think the relationship between scientific necessity and off-label use would have to be explored and unpacked further. But that's at least not what I intended by the statement that I gave about the principle of scientific necessity.

DR. FOST: Maybe even it's sufficient to say that we should keep those distinctions in mind.

DR. NELSON: Yes. There are a lot of examples of where we've gained further information once we've studied things that are in fairly common off-label use that have suggested that the doses or safety issues, et cetera. So that's a whole separate issue. But it's not to argue that absent that kind of research that there should be no off-label use. That would be a different argument.

DR. FOST: Yes. Okay. Other comments?

All right. So can we say anything of a summary nature about prospect of direct benefit?

It sounds like people agree that intent is an important component of it. And whether the prospect is reasonable enough or sufficient will depend on existing data, depend on the seriousness of the disease, depend on what we know about the side effects of the drug about whether it's likely to have risks or not. So all those things are

components of whether the prospect is sufficient to approve it, and self-evident that just because it fits in that category, it doesn't mean it's okay to go ahead. There should be something more than just saying it fits in the category.

Any other comments about that? Steve?

DR. JOFFE: I want to just go back to this issue of the population that's more at risk versus the population that's most able to consent, and just reflect back for a moment on the Jesse Gelsinger case.

And you'll all remember that the gene transfer intervention that was being studied in that case -- and if I remember correctly, it's one of the urea cycle defects -- I don't remember which. But -- OTC deficiency. That's right. So Gelsinger had a mild form. Gelsinger you remember was 18. And he had a mild form of the disease and had been able to manage it with dietary control

throughout his life with just a few exacerbations. There are infants with a much more severe form of the disease who don't survive infancy.

And the discussion at the time of that case was whether to do that study in the most at-risk population, which would be infants who clearly would not be able to give their own consent, or to do it in somebody like Jesse Gelsinger who was a young adult who could provide his own consent, but was much less likely to benefit from the intervention, recognizing that this was a first-in-human-kind of a study of a gene transfer intervention.

And the decision that was made at Penn was that sort of consent trumps benefit prospects. And you might say, although I don't remember reading anything about this consent trumps sort of who the target population is for the intervention ultimately. And there was a fair bit of debate about that

afterwards about whether that had been the right decision, with Julian Savulesco -- among others -- arguing that really it was inappropriate to do that in somebody who is at such a low likelihood of benefiting from the intervention and that consent should have weighed less heavily on the decisionmaking.

So this will come up in the particular context we're talking about among adolescent populations, for example, who's most able to give robust consent/assent -- whatever we want to call it. But this could even come up in terms of using young adults as subjects versus using children who are more at risk for the disorder or a severe form of the disorder, and yet less able to give consent.

DR. FOST: Did you mean to imply though in your comments that they made the wrong decision?

DR. JOFFE: I don't know if they made the right decision or not. But it clearly was one example where the distinction

between the two approaches sort of came up in very sharp relief, and a decision had to be made.

I don't know if there are others around the table have strong feelings about the way that that should have been done. But clearly a decision was made that in that setting at least, the ability to consent was the sort of highest value that the study had to live up to.

DR. NELSON: First a point of clarification. I was not at FDA at the time, nor was I at the University of Pennsylvania at the time. So my opinions have no basis in fact, I guess is what I'm saying.

What I find interesting about that discussion -- I think it was and is a legitimate discussion -- is what's often missing from that discussion is that the distinction there is adult pediatric. Often Jesse's viewed as a child.

And I think in the way in thatB-but

again, whether it should or shouldn't have been, the very regulations that lay out the prospect of direct benefit and those sorts of things are finessed in the adult setting. And the adult trial could go forward absent the same kinds of constraints that Subpart D provides. That was really the decision.

I think the more challenging question that I ask about population is less adult versus pediatric, but whether or not even if Subpart D applies where the one would begin to sort of frame the target in consenting population -- older adolescent, younger adolescent. I'm not suggesting we go there. But the issue in the OTC trial was simply could one do it at all under Subpart D, meaning what was the evidence in favor of prospect of direct benefit.

Since I don't know that data nor is that on the table, you can't answer that question. But the perception is somehow that Jesse was a child who made that decision which

is I think a misimpression. But that's I think how it has played out in the public sphere.

Having said that, Norm, I guess it's your chair prerogative about where you want to go over the next 12 minutes as opposed to break early for lunch. But that's up to you.

DR. FOST: Yes. Well, I was going to say I think the other cases -- particularly the case tomorrow morning -- will allow us to revisit these concepts. And maybe we can come up with some more generalizable statements near the end. And I think raising Gelsinger is just another example how cases make it easier to see where we think on this. So we may revisit that.

So I think cases help. And as we go through the other two, it may sharpen our conceptual focus.

I don't have any compulsion to sit here until 12:00 o'clock. So unless somebody

has some other points they want to make that we haven't covered, why we don't break?

And Carlos, do you want to tell us about lunch arrangements?

DR. PEÑA: Sure. If committee members can just stay after the meeting adjourns, we'll get you all to lunch.

DR. FOST: Other closing comments for the morning session?

DR. NELSON: I'd just remind people we'll be restarting at 1:00 o'clock. And the first thing at that l:00 o'clock is an open public session. And I guess at that point we'll learn if anyone has signed up.

DR. FOST: Thank you. See you at 1:00.

So committee should stay seated for a minute.

(Whereupon, the above-entitled matter went off the record at 11:49 a.m. and resumed at 1:04 p.m.)

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

(12:55 p.m.)

DR. FOST: Thank you all for returning.

So we now have a public session. Let me just get to my program. Excuse me.

So, we have a half an hour now for an open public hearing. And let me read the announcement for that. And to the best of my knowledge, we have one person requesting to speak, and then we have a written statement, which actually pertains more to the asthma study. So we're going to read that statement tomorrow morning, which is the next public session.

But at today's public session, we have one request to speak -- Dr. Michelle Lally from Brown University. So let me read the announcement, and then invite Dr. Lally to the microphone.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing of the Advisory Committee

meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any of the topics on the agenda related to sponsors or their products. For example, this financial information may include the payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages, you at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So with that, if Dr. Lally is here, welcome.

DR. LALLY: Thank you very much.

In terms of disclosure, I am working for the HIV Vaccine Trials Network, and they sponsored my trip down here.

In terms of full disclosure, I have also done some trials for Merck, and am a paid consultant and speaker for Merck, as well.

I am an infectious disease physician, and have run many clinical trials of HIV vaccines among adults, and am very interested in the issue of enrolling adolescents into clinical trials, so that we ultimately will have an indication for adolescents when we have the first HIV vaccine.

This hypothetical case has been very interesting, and I really applaud you for addressing this, and tackling some of the very complicated issues that, you know, are raised with this case, and with this whole field.

I don't want to get into too many specifics of different prospect candidates

that are out there, but would rather just go back to the hypothetical case that was presented. And I appreciate the comments that were made, but would just really raise the issue of, in the context of this phase 2 trial, if people are not comfortable enrolling adolescents into this trial yet, what do we do next? If this trial goes on to a phase 3 efficacy trial, which was sort of suggested, and then we see efficacy for adults, and then an indication and an approval for adults, what about the adolescents?

As was mentioned, the epidemic is affecting those in the 15 to 24-year age group. And this epidemic is one that infects 16,000 people every single day. And this disease is still not curable. And we don't know that it ever will be curable. So this is an important disease, and it has important public health implications.

I would argue that the day that we have an initial indication - an additional

licensed product - it needs to be licensed for adolescents, as well. And in fact, it is unethical if this vaccine is only licensed for adults.

The adolescents will be a target population for this vaccine, both domestically and, more so, internationally. But we need a regulatory path that will allow us to have a clear indication for adolescents on day one.

I think one of the important issues that has been raised as part of this discussion is that there are some silos that exist. There's the ethical silo, there's the regulatory silo, and there's the policy silo. But we need all of those people to talk to each other, and help us understand how we can have our initially licensed vaccine be given to adults and adolescents on the same day.

If it will be acceptable for us to extrapolate adult efficacy data down to adolescents, we can live in that world. But we need that world to not change on the day

that the adolescent and the adult indication comes forth. We need that laid out more clearly.

Alternatively, if that's not going to happen, in the world where we're considering what is prospect of benefit, I think, as was raised by Alan, if we are at this stage where we're conducting an efficacy trial, or where we're conducting a phase 3 trial, is that enough? Has that bar now been crossed where the scientific community feels that there's enough prospect of benefit for us to also include adolescents in that trial?

I'd now like to just turn the mic over to Jeff Safrit, who's with the Elizabeth Glaser Foundation. Is that okay? Yes.

DR. SAFRIT: Sorry. We kind of tag teamed this, but we didn't let Carlos know the specifics.

My name is Jeff Safrit. I'm with the Elizabeth Glaser Pediatric AIDS Foundation, and I have no financial hindrances

that would prohibit me from speaking in front of you today.

And again, I want to mimic what Dr. Lally's already said. I applaud you for having this discussion. I think it's critical.

The timing -- I wish we had had this discussion when the Phambili adolescent arm was being considered, and before the Step results came out, because I think any discussion that we have at this point on, obviously in the back of your mind you're going, well, we know that there's a product out there that's caused harm. And, you know, the FDA, you can say, at this case, and this case, the specific case of the Merck vaccine was very prescient, because they turned down an adolescent arm of a trial before knowing that the product might actually be harmful. That's wonderful, but the reasons for turning down that trial are what we really need to discuss today, and determine how we get to a

point where a trial such as that can actually be done.

So the Foundation, back in, probably as early as 2001 and 2002, started having conversations with the FDA in terms of how we could get to guidance around including pediatric populations in vaccine trials. And the Foundation's obviously interested in prevention of mother-to-child transmission, prevention of breast-feeding transmission. We're not going there today, obviously, because we're talking about adolescents.

But just to the point, adolescents, as Dr. Lally mentioned, are an extremely high at-risk population in sub-Saharan Africa, and in some cases, in discreet populations in the United States - in Baltimore, in New York and Los Angeles. There are very similar populations to what you find in South Africa in terms of the risk of HIV infection.

So just going back to the guidance that was issued by the FDA in May 2006, after

consultations with the Foundation and others, there are three bullet points that relate to the amount and kinds of data that need to be considered -- adult data that need to be considered when you're talking about including adolescents in trials.

Obviously, the first bullet and the most important one is that you really have to have strong adult safety and immunogenicity data. There's absolutely no question about that.

The second two points I think deserve more discussion, because they leave room for a lot of interpretation, and I think that's part of the discussion that's going on today. What is known about the investigational vaccine in terms of its relationship to well characterized vaccines, or novel vectors, or production methods, that's, again, very product-specific. But importantly, the relationship of the documented immuno responses to protection,

that is an area that we may never get to, because it's very possible that we won't have a correlative protection for an HIV vaccine prior to having a licensable vaccine. We may never know why it works. And when we find one that works, is that going to prohibit us from going down in age to test the vaccine in a population where it's absolutely critical to use that vaccine?

That's all I want to say. Thanks for your time.

DR. FOST: Thank you. Any comments, questions, discussion? Yes, Jeff?

DR. BOTKIN: I guess I want to clarify with Dr. Lally.

I think I agreed with almost everything you said, except perhaps the day one caveat. And is it your contention that we should not be pursuing adult data initially before enrolling adolescent subjects in safety and efficacy trials? Should we be - given the nature or severity of the problem in the

adolescent population - are you advocating that they be enrolled up front with these initial trials?

DR. LALLY: If we need to enroll them when we enroll adults into efficacy trials in order to have an initial indication for both adolescents and adults, than I'm comfortable enrolling them at that time.

Adults are at risk for HIV, too, so I don't think that we should not enroll adults into efficacy trials, but I think that, on the day that we have a licensed vaccine product, that label must include adolescents, and we need to figure out a way to make that happen.

DR. FOST: Other comments or questions?

If not - and no other speakers, I take it - I think we can move on.

Yes, Ben?

DR. WILFOND: You mentioned that there's another person who had something about the asthma. Is there any reason we wouldn't

want to hear that before we discuss asthma, since that'll be related to our conversation? Just a question.

DR. FOST: I think it was short, so we could do both.

DR. JOFFE: I wonder -- just the point that has been made, I think, very cleanly and compellingly that the ultimate goal is to have a vaccine if and when a vaccine is developed that is efficacious, and sort of understood well enough to be used in the adult population, that we ought to have it available for adolescents at the same time is one I want to endorse, and wonder if there is a counter-argument to the point that has been