

**JOINT MEETING OF THE  
PEDIATRIC ADVISORY COMMISSION  
AND THE  
PEDIATRIC ETHICS SUBCOMMITTEE**

FDA White Oak Great Room (Building 31)  
10903 New Hampshire Avenue  
Silver Spring, Maryland, 20993

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## ATTENDEES

ADVISORY COMMITTEE	PRESENTERS
Marieann Brill, MBA, RAC, MT, ASCP	Genevieve Laforet, MD, PhD
Mark Hudak, MD	Perry Shieh, MD, PhD
Christy Turer, MD, MHS, FAAP, FTOS	Brett Bullers
Douglas Diekema, MD, MPH	Erin Bullers
Melody Cunningham, MD, FAAHPM	Nicholas Bullers
Aileen Foley, MD	Donna Snyder, MD
Wael Sayej, MD	James McGough, MD
Steven Joffe, MD, MPH	PUBLIC COMMENTERS
Michael White MD, PhD, FACC, FAAP	Megan Polanin, PhD
Sarah Hoehn MD, MBe, FAAP	Delanna Thomas
Maria Birzescu, MD, MS	Anita Bullers
Rodney Levine, MD, PhD	Christine McSherry
Norman Fost, MD, MPH	Suzanne Gaglianone
Amy Celento, BS	Rebecca Majors
Richard Kryscio, PhD, MS	Jenn McNary
Samuel D. Maldonado, MD, MPH, FAAP	Brian Denger
Marc Moon, MD	Erin Bullers
FDA PARTICIPANTS (Non-Voting)	Jordan McSherry
Robert (Skip) Nelson, MD, PhD	Shelly Mays
Donna Snyder, MD	Dr. Neera Gulati
	Dr. Robert Dracker

## WELCOME AND INTRODUCTIONS

**DR. HUDAK:** Good morning. I guess we'll get started. Welcome to this joint meeting of the Pediatric Advisory Committee and the Pediatric Ethics Subcommittee. And I'm Mark Hudak, I'm the Chair of the PAC. Welcome to the members of the committees and the guests and to the members of the public who have come to listen to this discussion. I think we'll get started by just having the people around the table introduce themselves and move into the introduction of the meeting. We'll start. Dr. Snyder?

**DR. SNYDER:** I'm Donna Snyder with the Office of Pediatric Therapeutics Pediatric Ethics.

**DR. NELSON:** Skip Nelson, Deputy Director, Office of Pediatric Therapeutics.

**DR. TURER:** Christy Turer, Medicine and Pediatrics at the University of Texas Southwestern.

**DR. DIEKEMA:** Doug Diekema, Pediatrics and Bioethics at Seattle Children's Hospital and the University of Washington.

**DR. CUNNINGHAM:** Melody Cunningham, Pediatric Palliative Care, Le Bonheur Children's Hospital and the University of Tennessee.

**DR. FOLEY:** Aileen Regan Foley, Pediatric Neuromuscular Specialist, NINDS, NIH in Bethesda Maryland.

**DR. SAYEJ:** Wael Sayej, Pediatric Gastroenterologist, University of Connecticut.

**DR. JOFFE:** Steve Joffe, Pediatric Oncology and Bioethics. University of Pennsylvania and Children's Hospital of Philadelphia.

**DR. HUDAK:** Mark Hudak. I'm a neonatologist and Chairman of Pediatrics at University of Florida College of Medicine in Jacksonville.

**MS. BRILL:** I'm Marieann Brill. I'm the DFO for this meeting.

**DR. WHITE:** Michael White. Pediatric Cardiologist and IRB Chair at the Oxnard Health System and University of Queensland.

**DR. HOEHN:** Sarah Hoehn, Pediatric ICU, University of Kansas.

**DR. BIRZESCU:** Maria Birzescu, Anesthesiologist, NIH Clinical Center.

**DR. LEVINE:** I'm Rod Levine. I'm a neonatologist and I run a basic research program at NIH.

**DR. FOST:** Norm Fost, pediatrics and bioethics, University of Wisconsin, Madison.

**DR. KRYSICIO:** Richard Kryscio, Biostatistician, University of Kentucky.

**DR. MALDONADO:** Sam Maldonado, Pediatrician. And I'm the industry representative for the PAC.

**DR. HUDAK:** Okay. Thank you. We are here today to consider some questions that have arisen in the course of a review of a clinical protocol by the University of California, Los Angeles. And they have referred it to these committees under Code of Federal Regulations Title 21, Part 50, Subpart D. And there will be a lot of explaining about what all of these different numbers and parts of the regulations are so I won't elaborate on them now. But we look forward to a great discussion on these questions. I'll turn it over to Marieann to give an opening statement.

## OPENING STATEMENT

**MS. BRILL:** Thank you and good morning. The following announcement addresses the issues of conflict of interest with regards to this meeting and is made part of the public record. Today the Pediatric Advisory Committee and the Pediatric Ethics Subcommittee will meet to discuss a referral by an IRB of a clinical investigation that involves both FDA regulated products and research involving children as subjects. The clinical investigation is entitled A Double-Blind Placebo Controlled Multicenter Study with an Open Label Extension to evaluate the efficacy and safety of SRP-4045 and SRP-4053 in patients with Duchenne Muscular Dystrophy.

With the exception of the industry representative, all participants of the committee are special government employees or regular government employees from other agencies that are subject to the federal conflict of interest laws and regulations. The following information on the status of the Advisory Committee's compliance with the federal conflict of interest laws, including but not limited to 18 USC Section 208 of the Federal Food, Drug and Cosmetic Act, is being provided to participants at this meeting and to the public.

Related to the meeting topics listed in the meeting agenda, members and temporary voting members of this committee have been screened for potential financial conflicts of their own, as well as those imputed to them, including those of their spouse or minor children and for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, speaking, writing, patents and royalties and primary

employment.

Based on the agenda topics and the analysis of the financial interests reported, FDA has determined that members and temporary voting members of this advisory committee are in compliance with federal ethics and conflict of interest laws under 18 USC 208. With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interest is being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

Dr. Shieh has acknowledged that he has served as an investigator in clinical trials sponsored by Sarepta, including the topic before the committee. He has also participated in an ad-hoc advisory board by Sarepta. Dr. Shieh is not a special government employee. As a guest speaker, Dr. Shieh will not participate in committee deliberations nor will he vote. To ensure transparency, we encourage all voting and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

In order to provide the expertise required to adequately address the topic covered at today's meeting, Ms. Celento, Doctors Birzescu, Diekema, Foley, Fost, Joffe, Kryscio, Levine and Moon will be participating as temporary voting members. With respect to FDA's invited industry representative, we would like to disclose that Dr. Maldonado is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Maldonado's role at this meeting is to represent industry, in general, and not any particular company. Dr. Maldonado is employed by Johnson & Johnson.

Ms. Amy Celento is participating as the patient family representative, which is a voting position. We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement. The exclusion will then be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with the firms that could be affected by the committee discussions. Thank you.

**DR. HUDAK:** Thanks Marieann. We'll turn it over to Dr. Nelson who will give an overview of the agenda.

## **OVERVIEW OF AGENDA**

**DR. NELSON:** Thanks Mark. Since my comments are a little more extensive than I normally do, I thought I would make it from here instead of my seat. Because I think I'd like to acknowledge the contributions of a number of different parties to putting this meeting on. First and foremost, I would like to thank the Duchenne community for their constructive engagement in bringing this issue to our attention and in supporting getting this meeting going. And particularly, the parents and patients that are most deeply affected by this issue and those of you who are here that can bear witness to this proceeding.

Thank you. I'd like to thank the UCLA investigator, Dr. Shieh, and the IRB for their willingness to step up and to make this referral. There are many IRBs that

if you said do you want to send something to the FDA, would say no, in no way would we want to do that. And so I am certainly grateful for their participation in the success of this meeting. The sponsor, Sarepta, has been quite collaborative in putting the materials together and working with us around those redactions.

I'd like to point out -- I mean, I've been involved in these reviews in different roles since 1999. And in my knowledge, this is the first referral under 50.54 or the HHS 407 that involves a commercial sponsor. All of them have been academic sponsors. And so in this context, we've been balancing the ethical obligation for transparency with what I also consider an obligation to sort of protect commercial and confidential information that might give advantages to competitors. And so you may see in public documents that there's blacked out portions of the protocol.

We don't feel any of that information is in fact germane to the discussion of the issue at hand, but is trying to respect that balance. And I think the Duchenne community, I hope, would agree with me that when you look at the explosion of product development over the last few years, all of that is commercial activity. And so it's a very important, I think, approach that we need to take in terms of that balance. Now with respect to that, I will just remind the members of the committee -- the committee has seen the unreacted documents, so they are aware of the things that are in those documents that have been redacted.

But I'll remind them that, in fact, if they choose to reveal that in public discussion, that's a criminal violation of federal regulations as government employees. I won't go into what the fine or the imprisonment is, but I'm happy to answer that for you. You're under the same obligations as I am to protect that information. But again, I don't

think it's germane. Now of course the members of the advisory committee, I mean this meeting has been set up within two months of the referral. The referral came in March 15th, this is May 18th. And as you can imagine, in terms of the timing it takes to set up a FDA advisory committee I think that is relative light speed.

And so we're grateful for your carving out the time to be here on fairly short notice. Now that will also allow me to transition to an explanation about Dr. Moon's involvement and an illustration of the extent to which our staff has worked to put this meeting together. Last week, we lost the surgeon who was supposed to be here in person because of a family emergency. We were able to get Dr. Moon involved on Monday and do his conflict of interest within 48 hours. Which I never knew we could actually do at the FDA frankly. I didn't think that was possible. One day, you're saying one day? Okay. Even less, 24 hours. To me that was phenomenal.

And it really shows that putting on this meeting is a team effort. And I'd particularly like to thank at the beginning of the meeting, you know, Marieann Brill our Designated Federal Official, the people that have helped, you've met Shivana Srivastava and Sheila Reese at the front table. Other people that have helped, Euneka Joseph, of course, does all of your travel. And Donna Snyder, since I was on vacation for the last two-and-a-half weeks, had the burden of working through all of the details of this meeting and has done an absolutely wonderful job in putting that together. And, of course, Alyssa Polovoy (phonetic) helped set this up.

One of the reasons we were able to put this meeting together on such a short notice was putting it in the Great Room. They work carefully with us to make sure that this was a good setup. We've got other volunteers from other offices that are

helping. The Office of Health and Constituent Affairs, Salina Miller and Captain Steven Morin. We have help from the Division of Pediatric and Maternal Health, Lori Gorski and Captain Tammie Brent-Howard.

And, of course, other members from our office that are helping in different aspects. Betsy Sanford, who you may have met outside, Captain Terrie Crescenzi, who is helping get people over here, Dr. Cathy Lee, who is providing additional IT support to our audio visual and of course Dr. Jean Temeck. So, you know, it takes a team effort.

Now one other comment about Dr. Moon. Because of our need to get him on board quickly, he'll only be able to participate this afternoon in the discussion. But we thought it was important when we're talking about placement of a central venous port to have a surgical perspective on that if certain questions come up.

He has received all of the presentations and has been able to review that, but will not be on the phone until after lunch. I think the only other thing I want to mention is this happens to be Sam Maldonado's last meeting as the industry representative. There is a small token of appreciation that we provided. I don't know if you want to hold it up, Sam, and show everyone what you look forward to getting if you're a member of the PAC. But we certainly appreciate his service over the years.

With that, let me just briefly look at the agenda. There will be an opening presentation by Donna Snyder to set the context for the day and the issue. Then Dr. Shieh will present his perspective as the principal investigator at the UCLA site. We'll hear from Dr. Jim McGough, who is chair of the IRB that reviewed the amended protocol. And then I'm pleased to say that Nicholas Bullers and his parents, Erin and Brett, will present their perspective on this issue.

And then we'll have the open public hearing of which I'm looking forward to hearing people's perspective on this issue. Following lunch, there will be a presentation by Sarepta. And at that point, I will return to sort of give the charge to the committee with the questions. And then the remainder of the afternoon will be dedicated to discussion.

That's the agenda for the day and I'll turn it back to you Mark.

**DR. HUDAK:** Very good. Next on the agenda, Dr. Donna Snyder will educate us about this complicated section of the Federal Register.

## **FDA PRESENTATION**

**DR. SNYDER:** All right. The purpose of my presentation is to provide some of the ethical and regulatory background that led us to review today for the ESSENCE protocol, which is the acronym that we use for the protocol that Marieann described at the beginning of the meeting under 21 CFR 50.54. And here are the topics that I plan to cover during the presentation.

The additional safeguards for children under 21 CFR 50 subpart D, a description of component analysis, a discussion of the referral to the ESSENCE protocol, a description of alternative venous access methods or devices, the application of component analysis to ESSENCE and a brief overview of the questions to provide a basis for the discussion later in the day.

When an IRB reviews a protocol for potential approval, the IRB is charged with evaluating the risks and benefits against the importance of the knowledge that's

expected to be gained as a result of the subject participating in the research.

Adults may participate in research solely to contribute to knowledge gained as long as adequately informed of the risk. But for children, there are additional protections that limit the amount of risk to which children can be exposed on the basis of contributing to knowledge alone. Those protections are found under 21 CFR 50 subpart D in the Federal Regulations. IRBs must evaluate research in the context of these regulations and we'll be evaluating the ESSENCE protocol in the context of these regulations today.

Essentially, research in children can be thought of in terms of research that provides a prospect of direct benefit to the child or does not provide benefit. If a child directly benefits from participation in the research, higher risk can be tolerated. The risk and benefits need to be at least as favorable as any alternative treatments. This research is approved under 21 CFR 50.52 in the Federal Regulations. For research that does not provide direct benefit the risk of participation must be low, either minimal risk categorized under 21 CFR 50.51 or no more than a minor increase over minimal risk or 21 CFR 50.53.

For situations that constitute a minor increase over minimal risk, the children must have a disorder or condition and the research or intervention must be reasonably commensurate with expected medical situations. Although the research does not need to directly benefit the child, the research must contribute to generalizable knowledge about the child's disorder or condition. For all research conducted in children, permission of a parent or guardian and the assent of the child must be obtained.

Now there are situations where research doesn't fall into the categories that

I just described, and this is the reason we're here today. If an IRB reviews a protocol and determines that the research doesn't fall under categories 21 CFR 50, 51, 52 or 53 under subpart D, but determines that the research offers a reasonable opportunity to understand, prevent, or alleviate a serious problem in children, the IRB can refer the protocol to the FDA for review under 21 CFR 50.54. The protocol must be reviewed by a federal panel. Today, that's the Pediatric Ethics Subcommittee and the Pediatric Advisory Committee. The panel's recommendation is then sent to the commissioner of the FDA.

The commissioner can then determine that the protocol is approvable under the three categories on the previous slide, 51, 52 or 53 or could allow the protocol to proceed under 21 CFR 50.54, as long as the protocol is conducted in an ethical manner and parental permission and assent are obtained. Now we'll move on to discuss some of the concepts that fall into play as we evaluate research under the regulations, the first being direct benefit.

Direct benefit in a study refers to the effect of the intervention on the child and whether that intervention improves the health or well-being of the child. For example, providing a drug to treat a disease may result in direct benefit, but the additional medical care that may be provided as part of the study is not a direct benefit of the research intervention. In considering direct benefit, the level of evidence needed to make a determination that the child might benefit needs to be considered. For example, for a rare disease that only occurs in children and for which there are no other treatment options, non-clinical data may be sufficient to support direct benefit and to initiate studies in pediatric patients.

But for a disease that occurs in both pediatric and adult patients and where there are alternative therapies available for pediatric patients, we might require adult data on efficacy prior to allowing studies in children. Another consideration for direct benefit in drug studies is whether the dose is sufficiently large and the duration of therapy of sufficient length to see an effect from the treatment. And finally, for interventions or procedures, whether the procedure is part of clinical care, or if the procedure or intervention might impact clinical care, will weigh into whether or not there is direct benefit to the child.

Another important concept is that of minor increase over minimal risk. The concept of minor increase over minimal risk was developed by the National Commission in the late 1970s as part of their report and recommendations on research in children. This was part of a larger project to develop guidelines for the protection of human subjects in biomedical and behavioral research, which led to the publication of the Belmont Report -- we're losing our slides -- and ultimately to the development of subpart D for pediatric patients. The commission defined minimal risk as a risk that's normally encountered in the daily lives of children.

Examples would be something like a physical exam in a doctor's office or a single blood draw through a peripheral needle might be considered minimal risk. Should we keep going or should we -- okay. All right. I think some people have copies of the slides as well.

The National Committee defined minor increase over minimal risk to be a risk that goes slightly beyond the boundaries of minimal risk and poses no significant threat to the child's health or wellbeing. In situations where the risk is a minor increase

over minimal risk, the children must have a disorder or condition that will be studied. So healthy children could not be enrolled.

Minor increase over minimal risk is a limited risk that a child may be exposed to if there is no direct benefit to participation in the research, unless there's a review by a federal panel, as we're doing today.

When evaluating risk in a research protocol, all the interventions and procedures in the protocol need to be evaluated separately to determine if they meet the requirements under subpart D. This is a concept called component analysis. The concept of component analysis was supported by the National Commission and the concept is included in the preamble to the final rule for subpart D, published in the Federal Register in 2013.

The concept is fairly straightforward. Interventions that may result in a prospect of direct benefit are considered under 21 CFR 50.52, and those that don't result in direct benefit under 21 CFR 50.51 as minimal risk or no more than a minor increase of a minimal risk, under 50.53, unless reviewed by a federal panel. Okay. All right. I'll just keep going.

One of the concerns of not applying component analysis to all the interventions and procedures in a protocol, is that if component analysis is not applied we might allow procedure or intervention in a trial to move forward that exceeds the allowable risk. Applying the concept of component analysis led us to a review of the ESSENCE protocol today.

ESSENCE is a double-blind, multi-centered, placebo-controlled, 96-week protocol evaluating SRP 4045 and 4053 in boys with Duchenne Muscular Dystrophy,

who have confirmed deletion mutations that are amenable to skipping exons 45 and 53. Boys with DMD have an X chromosomally-linked gene defect in the gene that codes for dystrophin protein. Without dystrophin, the muscle is destabilized. This results in the characterized progressive motor weakness and delay seen with the disease. SRP 4045 and 4053 essentially bind to targeted pre-messenger RNA sequences and fill gaps at exons 45 and 53 where the gene defect occurs. This allows the gene sequence to be read by messenger RNA. As a result, a modified but functional dystrophin is then produced.

In 2015, ESSENCE was reviewed by the FDA. At the time of the review, the protocol allowed the use of a venous access port at the discretion of the investigator. After applying component analysis to the protocol, the FDA informed the sponsor that the risk for boys participating in the placebo arm of the study exceeded a minor increase over minimal risk and offered no prospect of direct benefit. The sponsor subsequently amended the protocol to preclude the use of a port at sites in the United States. Ports were still allowed at sites outside of the United States.

In March 2017, the UCLA IRB received a complaint from a parent of a boy having difficulty with IV access in the ESSENCE study asking why venous access ports were not allowed in the protocol. The IRB reviewed the protocol and determined that the protocol, including the potential use of central venous catheters, met the requirements under 21 CFR 50.54 as a reasonable opportunity to further understand, prevent, or alleviate a serious problem affecting the health or welfare of children. An amended protocol that included the potential use of mainline catheters, central venous catheters and implantable ports was then referred to the FDA for review.

My next comment is that this slide includes a schematic of the protocol,

which we don't have, noting the 96-week, double-blind, randomized period to study drug or placebo and the 96-week open label extension phase. But actually, I didn't have any further comments because Sarepta and a number of the other participants and people presenting today will provide much more information about the protocol than I was planning on providing.

Why do we need to discuss alternative venous access methods for patients with Duchenne's? Boys with Duchenne's have problems with venous access for a number of reasons. Their veins may be more fragile due to the use of steroids, they may have scarring from multiple blood draws in the past and access to veins may be difficult due to contractures and positioning issues. Here is our schematic in case you wanted to see it. All right. As mentioned earlier, venous access ports are allowed in sites outside the US, so the sponsor, Sarepta, does have experience in their studies with use of ports.

Sarepta reported to the FDA that over half of participations have had ports placed during their studies and that 40 percent of patients have required a port because of the loss of venous access during their participation. In one study two-thirds of the patients had ports implanted between 68 and 183 weeks of the study. Of note, ESSENCE has a 96-week randomized phase and a 96-week open-label phase for a total of 192 potential weeks for the need for study treatment. The numbers here were provided to the FDA during the review of the protocol, but I think Sarepta has actually updated numbers in their presentation for today.

Techniques to add in visualization, such as ultrasound and infrared technologies, vary in terms of their rates of success in non-DMD patients. And there are virtually no data in regard to the success of these modalities in DMD patients. This slide

includes some of the alternative venous access methods that are proposed for use in the ESSENCE study and the comparative advantages and disadvantages of the various methods. These include midline catheter, peripherally inserted central catheters or PICC lines, central venous catheters or CVCs and venous access ports or port-a-caths.

And I thought I would just describe a little bit about what these things are but I think, again, we have more detail in some of the presentations coming up today.

A midline catheter is typically placed in the antecubital fossa of the arm or essentially at the bend of the elbow and threaded up to a vein to the level of the axillary area or the axillary vein. These particular lines don't enter the central venous circulation. A midline catheter has a similar complication rate to a peripheral IV and doesn't require sedation for placement. However, these lines have a very limited lifespan of days to weeks. The lines are secured by a suture and then taped down onto the arm.

**DR. HUDAK:** I think we're pausing the discussion for a few minutes to get the technical people to fix the problem.

**DR. NELSON:** We have an unstable computer.

**DR. HUDAK:** And unstable connection, right?

**DR. NELSON:** Right. I guess. Maybe it's Hal in, what's that, 2001? We're well past that date though.

**DR. SNYDER:** Does anybody have any questions so far since we have this break? Dr. Fost?

**DR. FOST:** We'll talk more about component analysis I'm sure. But I'm not sure why it's part of the agenda. Because this is being reviewed under 50.54 which

says nothing about risk analysis. The only requirements of 50.54 are review by a panel such as this and sound ethical principles. All that risk analysis stuff is 50.53. I'm curious as to -- the analysis was great but I'm just curious as to why it even --

**DR. SNYDER:** I haven't gotten to that part.

**DR. FOST:** -- comes up to this.

**DR. SNYDER:** Because it applies to the placebo arm of this study in terms of that not falling under 50.53.

**DR. FOST:** Those considerations only come up if you're reviewing something under 50.53. That's not why we're here today. It's not being considered. We're here because 50.53 was thought not to apply and so 50.54 is being used. And 50.54 makes no mention of that sort of analysis.

**DR. SNYDER:** Well if you can't review the protocol under 50.53, or that aspect of the protocol, then that leads you down the 50.54 path, correct?

**DR. FOST:** Which is where we are.

**DR. SNYDER:** Right. So this is just a lead up to describe why we ended up referring the protocol under 50.54.

**DR. FOST:** Yeah. I think that's correct. Okay.

**DR. SNYDER:** Just to provide some background in terms of how we made the analysis and got to where we are today.

**DR. NELSON:** If people are making comments you need to say your name before the comment for the benefit of the transcriptionist. This is Skip Nelson that made that comment about saying your name before the comment. Like Kant said, you should behave the way you expect others to behave.

**DR. FOST:** Norm Fost. I'm the one who asked that question. If we're still on hold I just have a process question. The materials were fantastic. And thanks to you and everybody who spent so much time preparing them. They're greatly helpful. But I didn't see anything in there about human studies data. That is, are we going to hear today about signs of benefit in the children here and in Europe who have already had this product? Are we going to get some information on outcomes?

**DR. SNYDER:** In terms of efficacy?

**DR. FOST:** I'm sorry?

**DR. SNYDER:** In terms of efficacy of the product? Because the study is ongoing so we don't have that information yet. I mean, Sarepta may be providing -- yeah, they're not providing any of that. So we don't know yet, you know. There is another product approved that works in a similar manner, but we don't have any efficacy on this product yet.

**DR. FOST:** Thanks.

**DR. SNYDER:** Do we have any other questions?

**DR. HUDAK:** All right. We'll keep our fingers crossed on this one.

**DR. SNYDER:** We were thinking if we didn't make any progress we'd just do it the old-fashioned way and hand out paper copies. I know a number of people already have them. Okay. That's it. Okay. All right. Hopefully we can progress to the next slide after I finish this one.

I was talking about midline catheters and I talked about the advantages that they have a complication rate that's similar to a peripherally-inserted IV and that general anesthesia is usually not required. In terms of the disadvantages of these lines, they have

a limited lifespan in terms of the order of days to weeks.

And they're harder to manage in these patients because they're actually secured by a suture and often taped in place. And so they may be prone to being pulled out with activity or just by the tape coming loose. Now PICC lines are placed in a similar location to a midline catheter, but are threaded up to the central venous circulation typically to the level of the superior vena cava when they're inserted in the arm. These lines have a longer lifespan than a midline catheter on the order of weeks to months. I'm going to keep going through this slide.

Anesthesia may or may not be required, but due to the time needed to place these lines sedation is almost always required in young children. The infection and complication rate for PICC lines is higher than that for midline catheters and ports. The issues related to dislodging the lines are similar to that for a midline catheter.

There are a variety of different types of central venous catheters or CVCs, but these lines generally fall into two general categories, percutaneously inserted CVCs and tunneled CVCs. Percutaneously-inserted CVCs have a lifespan of days compared to tunnel CVCs, which may remain in place for months.

A tunnel CVC is placed under the skin to exit at a location away from the insertion site to better secure the catheter. Anesthesia is generally required for tunnel CVCs. The complication rates vary based on the type of CVC, but the complication rate is generally higher than that of midline catheter, PICC or port. These lines may be difficult to perform in some pediatric patients due to issues related to catheter and vessel size. And percutaneously inserted lines may be prone to coming dislodged.

A venous access port is an implanted device placed under the skin and

access through the skin to collect blood or to provide infusions. Ports have a lower infection rate than CVCs and PICC lines and can remain in place for an extended period of time, often for years. The disadvantage of these lines is that they require a surgical procedure for placement that's more invasive than the other options, and general anesthesia is always required for insertion. As noted in the previous slide, sedation or anesthesia may be required for insertion of some of these alternative venous access methods or devices.

The use of nontherapeutic procedural sedation in pediatric trials was discussed at a Pediatric Ethics Subcommittee meeting in March 2015. At that time, the committee didn't reach a consensus on whether nontherapeutic procedural sedation, which would include the sedation or anesthesia needed for placement of a PICC, CVC or port, would be considered to be a minor increase over minimal risk. But the committee did agree on recommendations that should be included in protocols where nontherapeutic sedation or anesthesia is required such that the risk to subjects would be minimized. Those recommendations are posted online and the link is included in this slide. And the recommendations are also included in today's briefing document.

**DR. NELSON:** Donna, just keep going.

**DR. SNYDER:** All right. Now that we've discussed the various issues with the protocol we'll apply component analysis to ESSENCE. Boys who receive active treatment in ESSENCE directly benefit from participation in this study. The risks of the use of alternative venous access methods in these boys are weighed against the benefits of the drug. For patients in the treatment arm, the use of an alternative venous access method or device is considered to be approvable under 21 CFR 50.52 as

providing direct benefit. Boys on placebo don't directly benefit from participation in the study.

The risks of the alternative venous access methods or devices cannot be weighed against the potential benefits of the drug, so they can't be evaluated under 21 CFR 50.52 as providing direct benefit. And the risk of procedural sedation must also be considered in these patients. The use of a midline catheter, which does not require sedation for placement and has similar complication rates to that of a peripheral IV, can be considered a minor increase over a minimal risk and approvable under 21 CFR 50.53. However, the use of PICC lines, CVCs or port-a-caths in DMD patients in the placebo arm, exceed a minor increase over minimal risk.

Additionally, these procedures are not reasonably commensurate with expected medical care for their disease. The potential need for anesthesia further impacts the risk determination. Consequently, the use of these devices is not approvable under 21 CFR 50.53 and requires review under 21 CFR 50.54 in order for the protocol to proceed.

So I wanted to review the questions. Just so that we have them for reference as the discussion goes on throughout the day. But I think it would be best if you could actually see them. Do most people have a copy of the slides? Okay. Let's just keep going. All right. The first question is a voting question.

And the question is, the use of an indwelling central venous access device in the ESSENCE clinical trial should be allowed. And if the answer is yes, the answer would also include that there are circumstances in which an indwelling central venous access device should be allowed in the ESSENCE clinical trial. And if the answer is no,

there are no circumstances in which an indwelling venous access device should be allowed in the ESSENCE trial. And then there's a second series of discussion points which are not voting questions.

If the ESSENCE protocol, as amended to include the use of an indwelling central venous access device, is allowed to proceed, please discuss the following issues:

A) Should the choice and timing of placement of a clinically-appropriate central venous access device be left to the discretion of the study site investigator?

B) Should the protocol include criteria for deciding when an individual study participant has difficulties with peripheral intravenous access such that use of a central venous access device may be appropriate?

C) If the protocol should include such criteria, what type of criteria ought to be specified? For example, the number of failed attempts at establishing peripheral intravenous access, the number of visits where there was difficulty establishing peripheral venous access or the use of alternative visualization technologies?

D) And finally, how should the burden of undergoing multiple failed attempts at establishing peripheral intravenous access be taken into account? For example, anticipatory anxiety and post-traumatic stress.

That concludes my presentation. And now that I've finished, does anyone have any additional questions? We're not going to discuss the questions for this afternoon, but just based on the presentation. Dr. Joffe?

**DR. JOFFE:** Donna, Steve Joffe here. Your discussion of the use of component analysis as applied to this case, is that strictly speaking a regulatory requirement, that that is the way one must analyze a case like this? Or is that the way

that the FDA has interpreted or applied the regulations, but it's not strictly speaking a sort of black letter application of regulation?

**DR. SNYDER:** I think that the FDA has taken the stance that component analysis is part of the regulations as they are written. And we've also, you know, included that in the preamble to subpart D when it was published in 2013. You know, I know there are other ways of looking at component analysis, but this is the approach that we're taking now. Any other questions? All right. Thank you very much for your time.

**DR. HUDAK:** Thank you. Thank you, Dr. Snyder. We will move on next, I think, with the presentation by Dr. Shieh from UCLA, who is the principal investigator of the study at that site.

## **UCLA PRINCIPAL INVESTIGATOR PRESENTATION**

**DR. SHIEH:** Good morning. My name is Perry Shieh. I'm from UCLA. And I am the site investigator for the ESSENCE study. Is this working? Okay. You're going to drive it for me? Okay. All right. These are my relevant disclosures. I have served as a consultant on an ad-hoc basis for an advisory board meeting that was run by Sarepta Therapeutics. I am also the site investigator for this study as well as a few other studies, which is the reason why we're here today. Travel for today's meeting was supported by the FDA. Next slide please. Is it not moving?

**DR. NELSON:** Well, we will work on trying to solve this problem. This is Skip Nelson. But since Dr. Shieh's slides were provided to us at the last moment it's not as if you have a copy of them. We really do need to get these displayed. You have a

copy of this morning's version? And people in the audience have a copy of this morning's version? Well then that's --

**DR. SHIEH:** It's probably not this morning's versions, but it's sufficiently similar.

**DR. NELSON:** Close enough? All right. Well, we're back up. We'll keep working on this, but let's do our best.

**DR. SHIEH:** All right. This is what I'm going to talk about in the next 30 minutes. I'm going to go through sort of the background of Duchenne Muscular Dystrophy so we understand the context of this disease. I'll talk about the rationale for exon skipping in 45 and 53, go through the highlights of the ESSENCE protocol and then talk about the challenges of implementing this protocol. Next slide please. Just going to have to go through. We're talking about Duchenne Muscular Dystrophy as a disease of boys that is X-linked and its mutations in a gene in dystrophin. And because of their inability to make this dystrophin protein their muscles degenerate through time. Next slide.

This is sort of a natural history slide that kind of gives you an idea of how the disease may progress in a typical patient with Duchenne Muscular Dystrophy. Next slide please. And there is something that's called the Reading Frame Rule which really helps us to understand how mutations might predict the severity of the disease. And so, to illustrate this concept I want to just introduce this other Muscular Dystrophy, Becker Muscular Dystrophy, which many of you are already familiar with. It's also caused by mutations in dystrophin, but it has a much milder course than Duchenne Muscular Dystrophy. Can you just scroll through?

There are a couple of references I provide here, Monaco as well as Aartsma-Rus, which goes through this Reading Frame hypothesis, which I'm just going to quickly illustrate in the next few slides so that you kind of understand. Because it forms the basis for how this drug is proposed to work. Next slide. So just as a review of genetics, you know, amino acids are coded by three letter codons in the genetic code. And this is the genetic code that was revealed probably about 50 years ago showing you how the three letter codons are mapped into amino acids. Next slide please.

Just to illustrate what the Reading Frame Rule is so everyone is on the same page, I decided to create a really brief sentence in English of three letter words to illustrate the Reading Frame. So if you can kind of just scroll through here. And I just numbered each of the different letters one, two, three, one, two, three, one, two, three. And if you go through -- just keep pushing. Yes. This, dad pet the fat dog. If you slip by one then you go to another frame which I can't read. Next and then just keep going. And then the third frame is three, one, two, three, one, two. This illustrates one, two, three, one, two, three, one, two, three as the correct frame.

If you go to two, three, one, two, three, one, you get gibberish. If you go to three, one, two, three, one, two, you also get gibberish. So you want to read genetic code from the correct frame. If you don't then you're going to get an incorrect message. Next slide.

This is the dystrophin protein cartoon which illustrates that it is a very large, long protein. And it links intracellular cytoskeletal elements of the muscle to a membrane-bound protein complex here. And this has been proposed to provide some structural integrity to the muscle. It allows to protect and repair the muscle.

And that's probably why mutations that cause dystrophin deficiency result in progressive muscle degeneration. Next slide.

It's a very large protein. And this is my, you know, attempt at showing what the genetic structure would be. It's got a lot of these exons.

And there are 79 exons in here. And I think to illustrate the Reading Frame you can just imagine that you can map out these one, two, three positions into various different places within these exons. And most importantly, when we're thinking about mutations we have to think about the transitions between exons. So between one and two or between two and three, that transition has got to be a correct transition. Can you move on to the next slide? It's not moving. Okay. I've actually put them in there. Okay. At the end of exon one for instance it's a position one.

And I actually went through and looked up all these things. At the beginning of exon two is position two. So that's a one to two transition. And then you can see at the end of exon two is position three, and at the beginning of exon three is position one. And then at the end of exon six it ends in two and then the next -- the beginning of the next page, you can think of it, starts in position three. So those transitions are important transitions. But if you have mutations that remove certain exons, and those transitions are disrupted, you are going to shift the Reading Frame.

Next slide please. And deletions are actually very common. This is just a list of the various different kinds of mutations and their prevalence's. And you can see that more than two-thirds of mutations in dystrophin are actually large deletions. Next slide. Next slide. For instance, a relatively common mutation would be a deletion of exon 50. Next slide. Next slide. If that disappears, then exon 49 is now going to splice

to exon 51 and that three to two is not an allowed transition. The transcript that's made off of this gene is now going to have a shifted reading frame after exon 51. And a result it's going to result in a shifted code which will now lead to gibberish so to speak.

Next slide. This gets to the question of Duchenne versus Becker because we're talking about milder versus more severe course of the disease. Mutations that have the more severe phenotype usually disrupt the reading frame or remove critical portions of the dystrophin protein. And you can see there are a lot of spectrum repeat type, that's what those orange ovals in the middle are in the rod domain, is what we call dystrophin protein. You could have internally deleted sequences if you preserve the reading frame and you could still have a relatively functional protein.

But if you have a disruption of the reading frame then that would actually result in a non-functional protein. For instance, if we have a patient where exon 50 and 51 are both deleted, so more of the gene is actually missing than the previous example, you might, at first glance, think that that would actually be a patient who would have a more severe phenotype because more of the gene is missing. But in fact, because the reading frame is preserved in this case, you have a three to one transition, sequences that are coded by exons 52 through 79 are now going to be in the frame.

This would actually predict a relatively functional protein. Mutations that preserve the reading frame, especially mutations in the central rod domain, would generally have a milder phenotype, such as Becker Muscular Dystrophy. This is the rationale behind exon skipping. Exon skipping is being proposed for a number of different therapeutic strategies. And the idea is that you can skip an additional exon by using an investigational product, in this case Morpholino anti-sense oligonucleotide.

And by skipping an additional exon you may actually restore the reading frame.

In fact, the first product that's been studied for this is known as Eteplirsen. It received accelerated approval last year. And that product actually is directed at skipping exon 51. And the idea behind that, that perhaps a patient that's missing exon 50, it's outer frame, but if we have a therapeutic product that can skip the splicing of exon 51 then you can have 49 now splicing to 52 and that would restore the reading frame. So just to show that a little more explicitly, I threw a bunch of numbers into these boxes pretending these boxes are exons. And if a patient is missing exon 51 you have a shifted reading frame, one, two, three, one, two three.

And then the site of the mutation then two, three, one, two, three, one; that would result in a dystrophin which is nonfunctional, generally, because it's truncated because it will hit a spurious stop codon. But if you have a drug that blocks exon 51, you can skip over exon 51 resulting in a restoration of the reading frame. And this could be an internally truncated but still relatively functional dystrophin protein. This is some of the clinical data that's been derived from the Eteplirsen studies. This is not a double-blind study. It was a double-blind study for the first -- I think it's the first 24 weeks -- but after that point it was open label extension.

And taking all the patients over four years, you can see that they had a gradual decline in the six-minute walk test. However, based on the experiences of clinicians who take care of patients with Duchenne Muscular Dystrophy, this is a much milder course than we would typically expect. And in red you can see is cohort of patients from Europe which we feel is much more reflective of patients, the natural course of patients with Duchenne Muscular Dystrophy. And there's a divergence of the

six-minute walk test over time. And many clinicians feel that this is pretty much in line with what we think may be clinical efficacy for this drug.

And a confirmatory study for Eteplirsen is currently underway. But it's received accelerated approval as of September of last year. The ESSENCE protocol has a different set of targets because exon 51 is really only a target for approximately 13 percent of patients with Duchenne Muscular Dystrophy. Now looking at skipping exons 45 and 53, the combination of the two would probably reach about an additional 12 or 13 percent of patients with Duchenne Muscular Dystrophy. It's a signal strategy but looking at different patients. And these are the products as they're named by the sponsor.

Similar to Eteplirsen, these products have a similar chemistry but are designed to block sequences in their respective exons that are required for splicing. The protocol combines all of the lessons that are learned from previous clinical trials on exon skipping. The previous clinical trials, many of them over a longer term at least, were done open label. But this has a true double-blind placebo-controlled design. The goal is to recruit 99 subjects combining the patients from two different exons with these two investigational products.

Based on guidance from the FDA, as well as a number of different studies that have been published, it is suggested that to show efficacy a two-year study is really quite necessary to be able to demonstrate efficacy on a six-minute walk test. And so this is the way it's been designed.

The revisions have really made the protocol a lot cleaner and perhaps able to distinguish the efficacy of this type of approach. It really is a four-year study.

There's a two-year double-blind, placebo controlled phase followed by a two-year open-label phase. Some details. The randomized two-to-one active versus placebo. These products all require IV infusion every week.

And to demonstrate efficacy, at least at the mile marker level, an open muscle biopsy is performed at baseline as well as at the one year mark at 48 weeks. At present time, as we've discussed, no implantable IV central venous access is allowed at US sites.

Some of the key outcome measures. As we discussed, six-minute walk test at one year as well as at 96-weeks for the final analysis versus the baseline. And an important outcome is the mile marker of dystrophin quantification. There are some protocol challenges as I'm about to summarize. And you'll hear a little bit more from some of the other speakers.

We began screening in 2016. We were actually the first site to begin screening. That reflects the UCLA site. Our first patient was randomized. I believe this is actually our index patient that's going to be speaking today. The most common complaint has been difficulty of IV access. That's across all of our patients have had some level of complaints about the IV access issues, placing a peripheral IV, sometimes a couple of peripheral IVs if it's a pharmacokinetic day. And the multiple attempts that are required to actually do that on a weekly basis is difficult. We have used some methods to really mitigate some of these issues.

We use Lidocaine cream for all of our patients for placement of IV access. And we have begun using infrared vein finders with some limited success. I think you'll hear in a little bit more detail with some of our other speakers. But, you know, among

the patients there are a few that have had some significant difficult IV access. There's quite a lot of suffering for the patients, suffering from family members. And these things are real concerns for us in addition to the pain that they're experiencing. Among the patients who actually have adequate IV access, some of them have actually described that they're becoming more difficult to find IV access.

They may have begun the study with no problems but then started to have more problems as the study has gone on. We have a number of patients who have behavioral issues, autism, OCD, which is common among Duchenne patients. And IV access can really be a struggle really even in patients where IV access is good, you know. It's just the barrier of dealing with the idea of being stuck with a needle, among them, is quite challenging for staff as well as parents. Dr. Snyder reviewed some of these options a little bit earlier.

I think that really the total implantable venous devices, the port-a-caths I think are really the most reasonable option to consider if we're going to think about alternatives to peripherally placed IVs. Because this carries the lowest long-term risk and these devices can actually be in place for a number of years.

This is our proposed alternative, at least my proposed alternative is a port-a-cath. There's a reasonable amount of experience with these patients. We have patients with port-a-caths placed in other clinical trials including some of the previous clinical trials or ongoing clinical trials that have been sponsored by Sarepta.

This didn't come out very well. But this is just to show you what a port looks like. You can see over there the little bell-shaped thing is where the needle would be placed. That's actually -- and then the catheter itself is then tunneled underneath the

skin to one of the central veins. We typically have been using the internal jugular vein. Port placement requires a surgical procedure under general anesthesia. I've seen it under a laryngeal mask airway and sometimes people use an endotracheal tube. The port is placed underneath the skin.

An incision is made here and the port is placed in here then it's tunneled underneath the skin up to this point. And using a Seldinger technique, this port is then placed into the internal jugular here. So, two incisions. One over here and then the tunneling, and then another incision over here that's placed. And the tip of the catheter is usually most commonly placed in the junction between the superior vena cava and the right atrium. In terms of using the ports, our nurses at UCLA have a lot of experience using port-a-caths. They're very comfortable with it. We really have nearly no complications.

I expect that the long-term complications with the port use are quite rare. I did look into some of the literature on it. Most of the literature on long-term port risk has actually been in the cancer literature. There's some rates of infection. I think I've seen quoted rates, you know, in the single digit percentages over 1,000 days. That's probably not in line with our experience, but I think that maybe perhaps patients who have cancer have a higher risk of infections in general. Port-a-caths also can be used in the place of phlebotomy for routine laboratory work. So that's really been quite helpful for a number of our patients in other studies.

The risks of port-a-cath in my read: They're the surgical complications, potential complications of the procedure itself, the surgical procedure, the procedural sedation or procedural anesthesia. And then patients with port-a-caths over the long-

term are probably at risk for infection as well as thrombosis. And I think it's difficult to gauge that in patients with Duchenne Muscular Dystrophy because they are not sick in the same way that patients with cancer are. It seems like the greatest risk of the port-a-cath may be actually in the procedural sedation and the procedure itself.

The study itself, right now we're performing open-muscle biopsies and these are generally done with sedation to sort of minimize the amount of additional sedation we're talking about. This can actually be combined so muscle biopsies and port-a-caths can be performed at the same surgical encounter, minimizing at least the risk of procedural sedation and anesthesia. I just want to propose an alternative way of looking at the risk/benefit analysis. I know that we talked about component analysis.

And it's been the opinion of multiple IRBs, as well as the FDA, that the ESSENCE protocol falls with, at least in the placebo arm as, you know, no prospect of benefit. However, this does not account for the prospective benefit that can actually be seen in the open-label extension. I think that that's certainly something that a lot of people, including family members, are considering as well. If you want to talk about the prospective benefit of this new investigational product, it's perceived that the opportunity to participate even in the open-label extension is an important one.

And so research subjects that are randomized to active treatment, there is potentially a prospect of benefit of four years of treatment. Whereas the research for subjects that are randomized to placebo have the prospect of benefit of two years of treatment as well as, if the drug is additionally extended or approved, they would eventually be able to lead into that. Risks of the port lie mostly with the surgical procedure. And so we're talking about essentially a fixed amount of risk with different

varying levels of benefit.

These are my concluding remarks: The ESSENCE study is designed to establish the efficacy of, what I think is, a promising investigational medication in a severe pediatric disease that has an unmet need. The study, I believe, in its current form is well designed and based on currently accepted recommendations and standards. The enrollment interest of the study really speaks, I think, to the enthusiasm of the patients and their families. The report I got earlier this week was that out of 99 patients being the target, they've randomized 30 patients across the whole study.

So that's about eight or nine months they've already recruited nearly one-third of the patients that they need to enroll in this study. And again, I'm just going to say one more time that, you know, there is potentially a prospective benefit if you're considering the open label extension. And going back to 21 Code of Federal Regulations 50.54 this clinical investigation, I think, does present a reasonable opportunity for further understanding in preventing or alleviating a serious problem affecting the health and welfare of children.

And I think the study, the way it's designed right now, is being conducted with sound ethical principles. I thank you and I'm happy to take questions.

**DR. HUDAK:** Okay. We will start with Dr. Hoehn. Go around this way.

**DR. HOEHN:** Sarah Hoehn. I had a question. You made a comment about sometimes they need one IV, sometimes they need two IVs based on if it's pharmacokinetics. I didn't know what the standard was for how often they would need two IVs. And the second part of the question was do they need blood drawing IVs? Because then you would have to use a bigger gauge. I just wanted more clarity among

how many IVs each time and if they also had to be blood drawing IVs.

**DR. SHIEH:** They need to receive the investigational product, whether it be active drug or placebo, on a weekly basis. I don't actually recall off the top of my head how often we required pharmacokinetic draws but they have to be drawn in a different limb. And just off the top of my head I don't remember. But typically there will be safety laboratories that need to be drawn probably every four weeks. And those safety laboratories can be drawn from the IV as it's being placed.

**DR. HOEHN:** Can I just clarify your answer? It's Sarah Hoehn again. If they have to have the pharmacokinetics from a different limb then if they had a port placed would they still need a blood drawing IV because they couldn't get the blood drawn the same place they're getting the infusion?

**DR. SHIEH:** Yes. They would still require an IV. They would still require phlebotomy because, you know, you can't draw it from the port.

**DR. HUDAK:** Dr. White?

**DR. WHITE:** Michael White. If you could help me a bit with the science. My understanding is we're using the six-minute walk test as our primary endpoint. And it seems to me, in just a reading of what information we have is, dystrophin production should be a reasonable endpoint, it's a secondary endpoint. Is it because the dystrophin produced, after the exon skipping, is not a perfect copy of dystrophin? It's imperfect dystrophin and so we need to correlate the two, the dystrophin produced with the six-minute walk test?

**DR. SHIEH:** Is your question why dystrophin quantification is not the primary input?

**DR. WHITE:** Yes. Basically, yeah.

**DR. SHIEH:** I think that in order to conduct drug efficacy studies in accordance with guidelines from the FDA, it needs to be a clinical endpoint. I think that a number of us really believe that dystrophin quantification is quite a reasonable and valid biomarker endpoint. But I think in terms of whether this would be an acceptable registration enabling study, it has to be a primary endpoint.

**DR. WHITE:** But is the dystrophin that's produced after the exon skipping identical to native dystrophin?

**DR. SHIEH:** Oh, yes.

**DR. WHITE:** Or is it an imperfect compound because of the exon skipping?

**DR. SHIEH:** Yes. It would be an imperfect product if that's the way you describe it. It would be similar to dystrophin protein that you might expect from a patient with Becker Muscular Dystrophy. That's the scientific question.

**DR. WHITE:** We have to have the six-minute walk test to correlate with the fact that there is dystrophin production?

**DR. SHIEH:** Correct. Yes.

**DR. WHITE:** Thank you.

**DR. HUDAK:** Dr. Cunningham?

**DR. CUNNINGHAM:** Melody Cunningham. Thank you. Just one comment and then a question and a clarification on Dr. Hoehn. One comment just from my oncology experience is, from the port standpoint swimming and bathing are much easier for children. And that wasn't mentioned in the presentation. I think that's

important. It's been important to some of the children I've taken care of.

And then you talk -- and I was thinking about this as I was reading through the data before we came in -- but if the muscle biopsy is part of the initial, I can't remember whether it was a four or eight-week screening period, how could we assume that they'll be screened in and place the port at the same time. That's one of my questions.

**DR. SHIEH:** Procedurally in the protocol, the muscle biopsy is actually the last procedure that's done before -- it's the last thing that's done before the randomization occurs.

**DR. CUNNINGHAM:** This is Melody Cunningham again. So, they essentially would have been screened in. It wouldn't be that they were getting a port-a-cath put in and then would be screened out of the protocol?

**DR. SHIEH:** Correct. Yes

**DR. CUNNINGHAM:** Okay. And then just a clarification of Dr. Hoehn's question. So I understand you can't draw the pharmacokinetic levels from that port, but ports are drawable; and so for the other safety studies and labs, those would be able to be drawn from the ports?

**DR. SHIEH:** Yes. That's correct.

**DR. HUDAK:** Dr. Fost?

**DR. FOST:** Norm Fost. You mentioned at the end some recruitment problems. Do you know that that's related to the venipuncture problem? And second, from Europe or elsewhere, are there any parents that failed to enroll because they don't want a port-a-cath? So, two questions. Is the recruitment problem related to the

multiple venipunctures or if not, what is it due to?

**DR. SHIEH:** My comment about the recruitment is actually that I think that the recruitment is actually quite robust? Okay? Yeah. The recruitment is robust because I think that the patients believe that this is a promising type of treatment. Okay. And that speaks to the importance of the study. I don't think that there's a real quantitative recruitment issue.

I will answer your second question, which is that there are actually a number of patients who have hesitated to enroll in this study because their concerns of not being allowed to have a port because, you know, their son is autistic, you know. And it's difficult to deal with the behavioral issues that might come with phlebotomy and intravenous line placement.

**DR. FOST:** And have there been any dropouts because of the venipuncture access issue?

**DR. SHIEH:** Has there been any drawbacks?

**DR. FOST:** Drop outs. Has anybody dropped out of the study because of the --

**DR. SHIEH:** Nobody at my site has. I don't know if, you know, the sponsor might be able to answer if there's been any dropouts at other sites. But I do not know of any. It is a concern, though, that they won't be able to last two years or even four years without a port.

**DR. HUDAK:** Dr. Maldonado?

**DR. MALDONADO:** Yeah. Sam Maldonado. Question. This is really a US phenomenon. You said that you are doing this study in other countries in which

apparently they have a different ethics reasoning. Which are those countries and what are the ethics reasoning behind allowing this?

**DR. SHIEH:** So I only know what I've heard because I'm not directly involved in some of that information. But I've heard that there are sites in the European Union. And the European Union regulatory authorities are not requiring the restrictions on port placement. So they are allowed to use ports in the European Union.

**DR. MALDONADO:** This is Sam Maldonado. I understand. I mean they are allowing it, but on what basis? And maybe if you don't have the answer maybe the sponsor can answer why is it that that doesn't appear to be a problem there and it's a problem here?

**DR. SHIEH:** Yeah. I'll have to defer to the sponsor.

**DR. HUDAK:** Dr. Turer and then Dr. Nelson?

**DR. TURER:** Two questions. One, is there any contraindication to use of sedating agents for IV placement? You had mentioned, you know, the looking at visualizing the veins. But what about using a small dose of benzodiazepine prior to doing, you know, a major thing like a port? My second question is regarding risk of infection and problems due to use of steroids in these patients and there being differences in the musculature of even your blood vessels, right, that could impact having something within the vein.

**DR. SHIEH:** What was your first question again?

**DR. TURER:** First one was contraindications to use of sedating agents to really try to maximize the ability to just use a peripheral IV.

**DR. SHIEH:** I think, you know, in terms of what -- we haven't used

benzodiazepines to place. It is something that some of the families have asked for. We haven't done that because it is an additional -- you know, it could be arguably conscious sedation and we have hospital regulations on where you can, and the risks of doing conscious sedation even with low doses of benzodiazepines. That's of course open to interpretation. In terms of port placement, which I thought was part of your question, I believe it requires general anesthesia for the port itself to be placed. And then your second question was about?

**DR. TURER:** With the port, the risk of the port can differ by the population. For example, you mentioned patients with cancer.

**DR. SHIEH:** Oh, yes.

**DR. TURER:** Most of those patients are taking glucocorticoids which impact risk of infection. They also have changes to musculature. And there's musculature within veins which could potentially alter the risk when having a catheter placed within there for a prolonged period of time. I just wonder about what do we know about risk in patients on glucocorticoids or differences in muscle function with respect to the veins?

**DR. SHIEH:** Yeah. I think your point is well taken with regard to their increased risks on glucocorticoids. I don't think we have any data or numbers that I can speak to, at least I'm not aware of, that talk about their overall increased risk of infections.

**DR. HUDAK:** Dr. Nelson?

**DR. NELSON:** Just a quick comment in response to Sam's question. The way I would characterize some of these differences is not as ethical differences but

procedural one. The assumption under protocols interventions under 50.54 that they would be ethical as well. But we happen to have regulations that stipulate what IRBs can decide absent a federal panel review, which Donna went through. In Europe, there are no regulations along those lines and in Canada they have no regulations along those lines, they have guidance. And so, there's no restrictions necessarily on what an IRB could decide if they thought it was ethically appropriate.

I wouldn't characterize the differences as ethical, I would characterize it as procedural.

**DR. HUDAK:** Dr. Sayej.

**DR. SAYEJ:** Wael Sayej. Just two quick questions. The first one, as I understand that there is a variable presentation of DMD in patients in terms of severity and in terms of lung functioning in these kids. What is the effect of general anesthesia on these kids? That's the first question. The second question is how are the competitor medications administered? Are they also administered weekly through an IV catheter or port-a-cath or are they more spaced out or are they administered through different methods?

**DR. SHIEH:** So, yes. Your first question is about the variability. Yes, there is some variability in this disease. And I think that that speaks to the reason why there needs to be adequate numbers of patients enrolled as well as the two-year time period of the study in terms of the double-blind efficacy phase of the study. I think your question was more directed towards also the lung function and the risks of anesthesia. And I think your point is a very valid one. For most of our patients who are actually participating in the study, they have adequate pulmonary function.

That, at least, you know, and they're all screened by the anesthesiologist to make sure that the risks are not something that they are not comfortable with for the study. And they deal with the issues on a case by case basis. And your second question was? I'm sorry, I've already forgotten.

**DR. SAYEJ:** My second question was about competitor medications and how are they administered compared to this one?

**DR. SHIEH:** I think the investigational landscape of this disease has really flourished. A number of different investigational products by various different sponsors, some of them we wouldn't consider them -- most of them we would not consider direct competitors in the sense that they're not using the same type of strategy. It really depends on who you speak to.

But I think a number of physicians and experts in the field do believe that exon skipping is really a viable treatment option. A lot of our patients, and I think that that probably is the perception among the community of parents as well, a lot of them prefer to enroll them in an exon skipping study before they consider other types of strategies.

I don't know if I, you know, I don't know if everyone agrees with me. That is my perception about that. But, for instance, the Anti-Myostatin weekly subcutaneous is one of the products, monthly infusion is another product. There are a few of them that are oral. There are a number of different ones that are being proposed out there.

**DR. HUDAK:** Dr. Fost?

**DR. FOST:** Norm Fost. My recollection from when I used to start IVs, which is a long time ago, is that children with muscle wasting diseases where the muscle

has turned to fat that venous access is a much greater problem, their veins are much less prominent. And therefore, when people think about multiple venipunctures on children as being challenging, it's way more challenging. Am I remembering that correctly?

**DR. SHIEH:** That does seem to be my perception. But I don't think I'm the best person in the room to speak to that.

**DR. HUDAK:** Yes?

**DR. BIRZESCU:** Maria Birzescu, anesthesiologist. I would like to confirm, that's correct. It's way more difficult to obtain IV access on a patient that has myotonia and muscular dysfunction.

I also want to address the question regarding the draw anesthetic. Part of the exclusion criteria, these patients seem to be well screened and there are exclusions of patients that are vent dependent at nighttime as well as patients that have ejection fraction less than 50 percent. And that being said, I think it's also important to realize that as they are screened in they are considered and screened for anesthesia for the muscle biopsy.

That would be the ideal time to minimize the amount of anesthetic exposure by trying to perform both procedures at the same time.

**DR. HUDAK:** Dr. Levine?

**DR. LEVINE:** Rod Levine. One approach that was mentioned in the briefing materials was the possibility of converting the placebo group into a control group. And so it would become unblinded and there would be no infusion in that control group. Do you think, in your opinion, would that destroy the value of the study?

**DR. SHIEH:** I believe that the study was designed based on guidance

from the FDA in terms of what they feel would be a good registration enabling a good efficacy study. Previous studies have been done open label compared to an untreated arm. And I think that, you know, one of the major criticisms of those studies was the fact that it was not a true double-blind placebo controlled study. I think based on, you know, my understanding of what, you know, regulatory authorities have given guidance on, this study was designed based on that, those principles.

**DR. HUDAK:** Dr. White?

**DR. WHITE:** Michael White, New Orleans. As a follow-up to what he's asking, and help me because I'm kind of simple minded sometimes. The reason that we need to do a double-blind placebo is that we're using six-minute walk tests as the primary endpoint and the six-minute walk test can be influenced significantly, it's not a very objective measure. And so, if we don't follow identical procedures, the potential un-blinding of those who are in the placebo arm could inadvertently affect the outcome using the six-minute walk test. Is that the correct perception in this?

**DR. SHIEH:** Yes. I think that your statement is correct, that there are potentially motivational issues that may be involved. And that was part of some of the comments about previous studies. All of the most objective and non-motivational types of measures tend to be in the biomarker realm which is not a registration enabling outcome.

**DR. WHITE:** Okay. I guess FDA would not accept a biomarker in this circumstance?

**DR. NELSON:** There are no data at this point that show that dystrophin production is correlated to where it could be a validated biomarker and replace a clinical

endpoint. That's the whole point of the studies that are being done, to try and do that. That accelerated approval of Eteplirsen is based on the reasonable likelihood that dystrophin production could predict a clinical outcome. But there's a big difference between reasonable likelihood and does predict.

**DR. WHITE:** That was my understanding of the data from that study, was that it was done on the basis of the biomarker. And then the follow-up studies were using clinical markers.

**DR. NELSON:** There were clinical markers in the other trials as well. I mean, we can get into a discussion of the role of biomarkers. I'm not sure why this is going in and out but there's goblins in the audio visual. But yeah, dystrophin production is a promising but not proven biomarker, is probably the way I would phrase it.

**DR. HUDAK:** Dr. Cunningham?

**DR. CUNNINGHAM:** I call them poltergeists by the way. Melody Cunningham. Just another comment when we're thinking about the infection risk and talking about the corticosteroids. If we keep in mind that patients who are treated for about two years, sometimes longer, for ALL, Acute Lymphoblastic Leukemia, get corticosteroids as well as many other cytotoxic agents through the course of their therapy, so I think that we can put the infection risk in that context.

**DR. HUDAK:** Okay. Thank you, Dr. Shieh. Our next speaker to the group is Dr. James McGough who is representing the UCLA IRB.

## UCLA IRB PRESENTATION

**DR. MCGOUGH:** Well, good morning everyone. I'm Jim McGough. I'm a child psychiatrist and professor at UCLA and Chair of our Medical Institutional Review Board for Neurosciences. I'm also a former member of the FDA's Psychopharmacology Advisory Panel and currently a consultant. I am also a special government employee.

I want to give a shout out to Dr. Nelson and his team for responding to this so quickly as well as all of you for coming today. Patients are currently enrolled. The incidences that we are responding to here are ongoing, and I think a rapid resolution is really important to give them the relief that we think is indicated.

Just to mention, my travel today is being sponsored by UCLA and the FDA. I have no relationship whatsoever with Sarepta or any of its competitors. I have no involvement at any level with them for what that's worth. My thought today is, Skip asked me to sort of present the experience of our IRB and what we did. So basically, I'd like to just cover three things and then we'll have some time for discussion.

I'll quickly go over the background from the IRBs view of what has brought this forward. And it's good that I have my written notes. I'd like to walk you through actually the main issues in our process, basically the points we had. I believe you all have our minutes and other materials. So that's the in-depth description. But we actually spent a very considered amount of time, very good discussion about this. And finally, I'll just summarize what our conclusions were, which hopefully will inform your deliberations.

First of all let me just go over the background. We initially received the ESSENCE study for review in June of 2015. We did our initial review later that month.

We deferred it initially because there were some issues with consent that we thought were not properly addressed. It returned to us in August of 2015. We gave it our full approval.

A year later they had not yet enrolled any patients but we approved the continuation, and as Dr. Shieh said about a month later, September 2016, they enrolled their first participant. In February, we received the parent complaint which is the genesis of all this. And soon as I received it we scheduled it for our next meeting and we reviewed it on March 9, 2017.

Let me just briefly summarize the way we sort of view this issue. At the start of it, the FDA guidance for the study or the FDA determinations precluded the use of a port-a-cath due to the fact that there was risk without benefit in the placebo group for all the reasons discussed. Nonetheless, one UCLA participant's mother had complained of significant pain and stress resulting from multiple attempts at IV access on multiple visits. And I should say that Dr. Shieh called me almost immediately when he received this complaint. We discussed this really to try to solve problems.

In exploring it he was explaining that this one patient was getting five or more sticks. This was happening on a weekly basis. It was very stressful for the family. Vein access was poor as you indicated. And in spite of basically rolling the boy in EMLA cream, it was just not able to be done without significant distress.

In fact, as Dr. Shieh went on to say, all five of the UCLA participants were having similar difficulties. And he also mentioned that three of the five boys also suffer from Autism spectrum disorder which is an area I work in a lot. These can be very complicated patients to work with.

They're very sensitive, prone to react in extreme ways. And certainly, in unfamiliar settings with needle sticks, et cetera, it can be very difficult. Let me just briefly go over, for the point of being complete, who we are.

Our IRB is specifically devoted towards medical studies in the neurosciences. Our membership, who we are, composed of child psychiatrist, community reps, genetics, neurology, nursing, oncology, pharmaceutical services, psychiatry, psychology and pediatrics. And I don't know how many of you are on IRBs but we have a great working group. Everyone is very committed and we had very, I think, learned discussion on this.

Okay. Let me just walk through our various considerations. First of all, we reviewed the initial parent complaint and the group acknowledged the stress that was clearly being conveyed, that this was understandable. And what was becoming apparent in the actual conduct of the study, is that the weekly burden of multiple difficult sticks, in these really at-risk children who were really difficult to get blood from, really was a burden that was perhaps not fully considered when we initially discussed it. Again, the weekly issue over a course of 96-weeks of blinded treatment, this seemed like a very significant subject burden.

We also reviewed this initial concern. I had additional information that one parent actually offered on -- or one set of parents offered on their own to get a port-a-cath placed outside of the study. Dr. Shieh asked me what I thought of that. I actually advised him against that. That didn't seem appropriate.

But that conveyed again to us the degree to which parents who urgently wanted their children to participate would go to those lengths to ensure that this is done

in a way that was acceptable to them. We then, after talking about the occurrences and what was going on, we went in to specifically talk about well the risk versus benefits of using the port-a-cath technology.

And I think, Dr. Snyder, actually your slide excellently summarizes the various pros and cons of all the various techniques. I mean in general there's a concern about the need for general anesthesia. And then in general, again, with all the various forms of access potential for clotting, infection, need for removal later after the fact, the actual life span of the device and again, its potential for future use in open label studies. And those of you who are more expert in this can of course discuss this more later, but my take on your chart, Dr. Snyder, is that the port-a-cath is really the only access which is permanent, would sustain itself for the duration of the trial in terms of comfort of the patients likely to be optimal.

These, we think, should all be weighed in contrast to the initial risk of the general anesthesia. And then again, we also considered the risks and benefits of the other forms of access. And again, I think Dr. Snyder really covered the same points that we did -- infection, thrombosis, duration, the need to re-do the event, et cetera. Okay. Dr. Shieh also provided us with his recommendations for what he would do if he were running things in terms of the parameters that he recommended be employed in terms of actually moving to the step of port-a-cath.

And basically, what he proposed was that this system would only be used in patients with quantifiable, demonstrated problems with IV access. He specified this further in terms of operationalizing three or more attempts at two consecutive weekly visits or five or more attempts at one visit. Which again struck us as being a very

difficult burden to endure. And then also at our site at least these would only be -- what's the word? These only would be put in by people experienced with the procedure. And I think it might have been Dr. Fost earlier -- no it was actually Dr. Snyder mentioned, to some of your discussion later in the day, I think, this is a starting point at least for actually, again, kind of a designated criteria for moving out of IV access into port-a-cath.

And the only other aspect I could say is that, from our IRBs view at least, in terms of the question about who should make that determination. We at least, we have working relationships, we know our investigators. It's our starting point that we believe investigators just like IRB members are concerned about patient welfare, they're committed to ethical research. And this patient population requires a huge amount of sensitivity and support. And we would be very comfortable with the investigator at the site making that determination in consultation with the parents, providing full disclosure was included and following the criteria such as Dr. Shieh has recommended.

Okay. One of our members is a neuro oncologist who is very experienced using the port-a-cath device clinically and in research. She was able to provide further information, at least as to its performance at the UCLA site. And at UCLA, this is only performed at the Clinical Translational Research Center by expert people experienced with the procedure. Our occurrence of an infection, thrombosis, post-operative complications, I don't have them specifically quantified, but in general they are rare.

We would train parents. It would be part of informed consent, including information on how do you monitor for infection, what you do if you use the signs of infection. These patients are assessed weekly at the clinical visits, so there's opportunity

for follow-up. And again, a single placement of the port-a-cath is likely to be sufficient not only for the double-blinded study but for the open label treatment in which everyone gets active medication. That's the, I think, gist of what we talked about. Let me now just summarize what our conclusions were.

We were very concerned about the potential risk of weekly trauma and undue psychological burden because of participation. And perhaps because this is my area, but iatrogenic PTSD is a known phenomenon. These children are going to be experiencing increasing medical interventions over the courses of their lives. To traumatize them about the clinical setting just makes no sense. I think the risk of PTSD, the risk of psychological stress is very significant and we were very concerned about that. The risk of this sort of medically-induced trauma also -- it hasn't happened at least at UCLA so far -- but the risk for drop-out or early termination is, I think, a real one. Ninety-six weeks is a long time.

And of course, if participants drop out that's going to undermine the validity of the whole study. And then all the risk that everyone has shared in really could become a moot point if there's a lot of dropout. So that's another sort of concern as to why we think something needs to be done about this.

It was our determination mostly because the comfort and duration of a port-a-cath, to us, was deemed superior than the other means of access in spite of the need for general anesthesia, number one.

It was our sense that we were comfortable, at least, with the proposals Dr. Shieh was making in terms of how he would operationalize the movement from IV access to a port-a-cath. Again, of course, with full parent and participant consent and

assent. If it were not -- and I think this may speak somewhat to what Dr. Nelson was raising and I think what Dr. Foster or Dr. Maldonado was going to -- were it not for the previous FDA determination, we would have been comfortable seeing this as a minor increase over minimal risk. Now we didn't go there, of course, because of regulations. That was not our choice.

But I think just in terms of our ethical weighing of the issues, we would have been comfortable seeing this as a minor increase over minimal risk. In terms of the risk benefit analyses, I think as Dr. Shieh said, there's certainly -- you cannot argue there is any difference in risk of the procedure based on what treatment you get. You're going to get sedation, you're going to get the cath placed prior to getting any treatment. The risk for everyone is the same. We could argue somewhat about the potential for benefit. Let's remember that this is a condition with dire outcomes, there are no established treatments.

I think we are hoping that this active treatment is worthwhile. But let's be honest, I think we very much have equipoise in this study. If we knew this treatment worked we would give it to people, but we don't.

I think to some degree, to say that the active treatment group benefits, is maybe hopeful than factual at this point. In our view, I think there's more equipoise between the two groups than one might think. And of course, everyone rolls into open label treatment eventually. Everyone will ultimately have whatever benefit is present in the active drug by having the port-a-cath placement.

We decided unanimously that the ESSENCE investigation represented a reasonable opportunity to further understand, prevent or alleviate a serious problem

affecting the welfare of children. Were it not for, again, the previous determination based on the regulatory interpretation, this would have been acceptable to us had we had the opportunity to actually come to a conclusion about it. And as such then we recommended it to this panel for consideration under 50.54. And that is where I'm at. I'm happy to answer your questions.

**DR. HUDAK:** Dr. Diekema?

**DR. DIEKEMA:** Yeah. Dr. McGough this is Doug Diekema. I have two questions and I'm revealing my hand a little bit here with this first question. But it's unclear to me that multiple sticks over the course of 96-weeks is a minor increase over a minimal risk. And it's unclear to me that that's any less burdensome or risky than having a port-a-cath. I'm curious as to why your board decided the port-a-cath required a 407, but the multiple sticks did not. So that's question number one. Question number two relates to the criterion that you outlined that you would use in deciding who would get a port-a-cath.

And again, since so much of the burden related to the IV sticks is psychological, posttraumatic stress, et cetera, it's also unclear to me why you would require that patients wouldn't need to get to the point of multiple sticks, multiple failed attempts, as opposed to actually simply a parental request.

**DR. MCGOUGH:** Okay. I think in part we're all working -- you know, the FDA in its previous review came to some regulatory determinations which stand. I mean, that's the background we're working in. Of course, when we review the protocol, the protocol says IV access. It's only with our experience as the trial has ensued, that we've understood that IV access is not the simple put a hep-lock in and you're done with

it and you can move on. I think it's presenting a much greater burden than we appreciated. I don't think it was such a great burden, again, given potential benefits that we needed to stop.

But we're very concerned about this because the proof's in the pudding. And I think what we're learning is that this is a real difficulty and that perhaps it does shift how we should think about this a little bit. To the second point. Should you allow this or should the FDA after your determinations allow this? I suspect Dr. Shieh and the sponsor will come up with a protocol that's satisfactory initially to the FDA. I mean, my sense of one of Dr. Snyder's questions was that should there be some standards? And this is for all of you to weigh in.

Or should this be a choice that, you know, parents could be fully informed at the get go, along with their children, and they could make a decision at entry. But I think that's something for all of you to weigh in and then for the sponsor and the FDA to work out. I would be happy with that because I'm seeing what's going on. But again, there are multiple -- I think there are competing issues.

**DR. HUDAK:** Dr. Levine?

**DR. LEVINE:** Following up on this, two questions in your comments. I want to focus on newly enrolled patients, not those who are already in it. It seems to me difficult access is going to be 100 percent in this group. You can discuss exactly when that occurs. So did the committee discuss the possibility, as already mentioned, to minimize anesthesia risk of allowing with patient and parent consent implantation at the time of the biopsy?

**DR. MCGOUGH:** I think, again, my sense of it is that the FDA has laid

down a constraint. And, you know, it would be up to us to review a proposed amendment from the sponsor and the PI. We in fact, I think, could well be comfortable with that. But I think the whole reason we're having this meeting is by its interpretation of regulations this is what's required before we can do that. But then again, that's why I'm glad we're meeting early. And I'm hopeful that we can move on this quickly because people are in progress and people are being enrolled.

**DR. HUDAK:** Dr. Cunningham?

**DR. CUNNINGHAM:** Melody Cunningham. Thank you. So to dovetail with these last two questions and comments. We have to remember that after the trauma and anxiety of multiple IV sticks, a port isn't an end all be all. It still requires a needle, it's up close to the face. There's a lot of fear involved in that. And so, I think, that should roll into our consideration of whether parents know ahead of time that their children have significant needle phobia. And that that might, you know, be something that should come up in the beginning. And not put them through the anxiety and the fear of multiple sticks and then, oh, by the way, we're going to put a needle in a port that's quite close to your face in a child who may have some fear of new experiences.

**DR. MCGOUGH:** I very much appreciate this. And again, I speak also as a child psychiatrist. But people can be conditioned to, you know, allow things to happen. And I think, again, the pain and the distress of multiple, multiple sticks in tender arms is far greater than a simple routine. And, you know, we condition people to be able to tolerate an MRI which is also a problem with children with autism and anxiety. I think that's a more manageable risk, but a very valid one. And again, I think that would have to be part of the whole informed consent process.

**DR. HUDAK:** Okay. Ms. Celento? Maybe you could take the opportunity to introduce yourself?

**DR. CELENTO:** Yes. Amy Celento. Patient representative. And I apologize for being late. I was going to raise the same question that Dr. Cunningham raised. And to your point about conditioning, I guess what do you find in terms of conditioning a pediatric patient to tolerate a procedure? What kind of timeline is that? And the second part of the question is I'm not sure some of these children will be able to assess sort of like, well this is less traumatic than getting the five IV sticks. I mean, I'm not really sure they could draw those conclusions. I don't know if you can respond to those.

**DR. MCGOUGH:** Well, first of all I think we think fully informing people of potential risks is critical. Are you a member of the Duchenne's community as well?

**DR. CELENTO:** No. Actually, more so the thalassemia community. I have quite a lot of experience hearing about patient's port access for transfusions.

**DR. MCGOUGH:** Similar things?

**DR. CELENTO:** Yes.

**DR. MCGOUGH:** The Duchenne's community is very active, very supportive of each other really in an incredible way. But I think a full understanding of the risks is just critical. We are successful -- again, we scan very anxious kids. We have mock scanners, we work them through that. I do a lot of medication trials. Getting seven-year-olds to swallow pills can be a real challenge, but we have ways to gently sort of do that. So I think that is a manageable issue. Again, I think in consultation with the

parents and their understanding of their child, I think we can come to the best conclusion that one could.

**DR. CELENTO:** Okay. Thank you.

**DR. HUDAK:** Dr. Cunningham?

**DR. CUNNINGHAM:** Melody Cunningham again. Just to clarify. I guess I was suggesting if it wasn't allowable at the get go to place a port that use of other ways to manage this new access, perhaps child life specialists, perhaps some of the things that you do, would be reasonable. Placing the port wouldn't take away all of the fear and anxiety. I don't know if I was clear in my first statement.

**DR. MCGOUGH:** Possibly. And I think your point is very well considered. I should say though, at least the Duchenne's Center at UCLA has a very multidisciplinary team who is very, very much involved with these patients. We have child life specialists, we have other people. So I think the resources are available to deal with that. And again, from our IRBs perspective, I think we would find that acceptable.

**DR. HUDAK:** Dr. Joffe?

**DR. JOFFE:** Yeah. This is Steve Joffe. I'm not sure if this is a question for you or the sponsor or perhaps both. But I'm wondering if there was discussion, if in fact based on the vote of this committee and the decision of the FDA and the final decision at your IRB, if the placement of the port is -- if the protocol is amended to allow placement of a port, if there's been the discussion of who would pay the cost of port placement, port removal and any complications that came up related to the port? Would that be paid by the sponsor?

**DR. MCGOUGH:** Well I think the sponsor could weigh in on that. But

it's our usual position that all research related expenses need to be borne by the sponsor. There would be no reason, from my view, to make the families bear that cost or insurance bear that cost. But they can speak for themselves later. I suspect that the cost of this is minimal compared to the costs of failure of the trial.

**DR. HUDAK:** Dr. Maldonado?

**DR. MALDONADO:** Sam Maldonado. Thank you for the presentation about the IRB and UCLA. But I suppose that there are other IRBs in the United States. Is your position representative of those other IRBs or maybe the sponsor can comment?

**DR. MCGOUGH:** I don't know. You know, I think that part of the beauty of IRBs is they reflect local norms. And I think some of the guidance is vague and we come to our own determinations. But I think we, you know, there are IRB standards and conventions and I think we generally fall well within that. I think if this were presented, I suspect other IRBs would come to similar conclusions. But if not, they wouldn't approve this at their site. I mean, I think that would be their choice.

**DR. MALDONADO:** Thank you. This is Sam Maldonado. I was just trying to get a sense of is this something that the community -- I suppose the community is very supportive, but also the researchers in general. Not just UCLA, but do researchers believe it's in their best interest of these participants and these patients in general? And that's why I asked my previous question about the other IRBs outside the United States. Because at the end of the day, the question that is being asked of the advisory committee is not a procedural one, it's an ethical one.

**DR. MCGOUGH:** And I was going to just say, first of all, you'll be hearing from a family in a couple of minutes. But to your earlier point, I think again, we

are working within our regulatory schema here. But clearly IRBs in Europe have found this to be acceptable. So that may be some indication about sort of the general ethical acceptability of the procedure.

**DR. HUDAK:** Dr. Sayej?

**DR. SAYEJ:** Wael Sayej. I think perhaps the biggest question here is the ethical considerations and the placement of a port-a-cath, for example, during general anesthesia and obtaining the biopsy in patients who will be receiving placebo versus actually receiving the actual drug. I think that's probably one of the main reasons why we're reviewing this today. Not just because patients with DMD are receiving this medication on a weekly basis and are having a tough time with the IV sticks, for many people it's a no-brainer that those patients would require something more of a permanent access. But if they're only receiving a placebo then the ethical question I think becomes more of a bigger issue.

**DR. MCGOUGH:** Well I think that's exactly the point. I would encourage you to keep in mind though that everyone enrolls into open label treatment. Eventually, everyone will get open treatment. If that weren't part of this protocol we would probably have had concerns. Although again, since there are no treatments, you know, there's not a lot of choice. But I would really encourage everyone to keep in mind that on the single study, looking at that, you might come to that conclusion. But everyone is going to get active treatment.

And a port that is placed initially would not only decrease all the psychological risk, but would be usable and likely to provide whatever -- or facilitate whatever benefit is present in the active drug once they roll over into the open-label

phase.

**DR. HUDAK:** Dr. Turer, you have the last question before we move to the next presentation.

**DR. TURER:** Christy Turer. I was very struck by your point that there is clinical equipoise. And I think that it is critical that we have placebo controls. In the adult world, a great example is when we tested the drugs that increased HDL and we actually found out that they increased mortality. I think that this is absolutely critical that we maintain that in our clinical trials.

My question is regarding the number of peripheral sticks. I think it is important that we convey to families that there are still going to be peripheral sticks related to the pharmacokinetic studies.

I had documented that there are, in the course of this trial, at least 36 blood samples. That they occur at least once a week for the first eight weeks, again at 12 weeks, then every four to 12 weeks. And I guess this is not going to be something that you can answer, but I think it will be important to lay out the number of times these children still are going to require a peripheral stick for those pharmacokinetic studies. This won't alleviate that.

**DR. MCGOUGH:** I'm a fanatic advocate for fully informed disclosure in simple language. So that would certainly be what our IRB would look to. That things are clearly and fairly and simply stated so that the participants understand what we're doing. Thank you.

**DR. HUDAK:** Thanks, Dr. McGough. That was very enlightening. I think our next presentation we have a family, the Bullers family. Is that correct? Close

enough? Look forward to your observations.

## PARENT AND PATIENT PRESENTATION

**BRETT BULLERS:** Good morning everybody my name is Brett, it's Bullers, if you care. I'm Brett. That lady up there is my beautiful bride, Erin. And this big guy right here, this is little bull. That way we keep it simple. This is Nicholas. And as you all can tell he's living with Duchenne Muscular Dystrophy every day. And earlier this month he just turned 14-years-old, and that means a lot to us.

Well, we're here today to present on the patient and parent perspective of families participating in Sarepta's randomized double-blind placebo controlled trial of exons 45 and 53 and the skipping compounds that is the topic of today's meeting.

In September of 2016 our family decided to enroll Nicholas in the exon skipping study called ESSENCE. The families of two other boys participating in the ESSENCE trial are here today, in the audience, including his good friend. Where did Dawson go? There he is. He's right there. So, Dawson is here too. Nicholas does receive weekly infusions as part of the study at UCLA Medical Center under the supervision of Dr. Perry Shieh. We are one of the families who struggle with the peripheral venous access issues and Nicholas is elated to have his voice heard today.

We would like to provide some perspective on the experiences of patients with peripheral venous access issues in this study. And also, we would like to share how families with children affected by serious progressive illnesses like ourselves weigh the benefits and risk of serious medical decisions like port placement surgeries. We hope

you will consider our perspective when evaluating modifications to the protocol.

After Nicholas was diagnosed, just before his fourth birthday, he had to learn to swallow pills and that was not easy. But it was done. We were told also to just take him home, just love him, there was nothing else we could really do for him.

Well we disagreed on that. And we just knew that there had to be a better path for us to take. So we did seek out some of the best medical experts in the field of Duchenne. We were determined to keep him as healthy as possible because we just knew hope was on his way.

For nearly a decade we've been waiting for a treatment that could change the course of Nicholas' life by slowing the progression of Duchenne. Although that treatment has come with a burdensome protocol that includes two muscle biopsies -- and he'll show you the scars -- and a 96-week placebo risk, we are dedicated to giving Nicholas the best opportunity to maintain his muscle function.

Since UCLA was the first site to open, and time was running short due to the exclusion criteria, we decided to make the trips every week from Los Angeles with hopes that a site closer to our home in Houston would open soon. We often rotate who takes Nicholas, but he never gets a break. I mean it's an exhausting schedule.

For the last 34-weeks he's made the hour drive from our house to the airport and has a great time sitting around there as I'm sure you all know. He's actually friends with the TSA agents. And it's a nearly 4-hour flight that he makes. He hustles to the hotel just to get a quick night of sleep and then it's over to the infusion center.

And it's a day and a morning of needles. And we don't know how many and he never knows how many times are they going to get me today. If everything goes

according to schedule it's back to the airport, home, and then you do it all over again the following week. And my wife, Erin, she is going to be the one who primarily accompanies him to Los Angeles. She wants to share the information on the actual infusion process.

**ERIN BULLERS:** Good morning. The weekly infusions are administered through an IV, preferably in one of the main veins in the arm. However, many Duchenne patients do not have good peripheral access. I would like to emphasize, Duchenne boys lack the protein dystrophin in all tissues, including the veins and tiny muscles inside, which control the flow of blood. Add steroids and superficial inflammation, along with fibrosis and peripheral venous access, can cause major difficulties and pain. Quite often, other options to gain access during a clinical trial or other hospital visit must be utilized.

This has been our experience as Nicholas has been infused through the back of his arm and hand. Other peripheral access points include the foot or neck. I will never forget infusion number 15.

Nicholas and I arrived at the infusion center at 8:00 a.m., it was now 11:00. Three hours had already passed. Nicholas had three nurses at his side, each attempting to locate a vein. He was poked and prodded seven times. I could see how much pain this was causing him. Tears were rolling down his face while he was doing his best to stay calm. I am stressing about missing our flight. Even worse, what if the nurses can't access a vein? Will he have to miss an infusion? Could this cause him to be put on clinical hold or dropped from the trial?

Sometimes the kids in this trial even blow veins while being accessed. This

has only happened to Nicholas once and the blood went everywhere, even all over his special blanket that keeps him calm. Other children in this trial have experienced one or more blown veins. Nicholas manages to remain calm during this experience, but there are other boys who have less tolerance due to ADHD, OCD and sensory issues. We will now play a video showing a recent incident where Nicholas was repeatedly stuck in an attempt to gain peripheral access during his 32nd weekly infusion visit.

You will hear the TV playing in the background. We turn it on so Nicholas has something else to focus on during access.

### **PLAYS SHORT VIDEO**

As you see, Nicholas' weekly infusions have become unbearable in recent months. Nicholas would like to share with you how his participation in the ESSENCE trial is affecting him both before, during, and after infusions.

**NICHOLAS BULLERS:** Thank you for allowing my voice to be heard today. More airline miles, yes! I am not sure if I know when it's the end of infusion and the beginning of another. As soon as I get home from one trip I am preparing for the next. It is okay because I really want to be part of this trial. Often, the nights before infusion I don't sleep well. I get nauseous. I nearly drown because my mom and dad make me drink so much water. I'm anxious whether or not I will get poked numerous times. I listen to soothing music to keep me calm. My sweet nurse, Lily, is always sweating because she is working so hard to only poke me once.

No matter how many times they poke me, they have to get the tape off. Man does that sting. After the four-hour infusion is over I rush to the airport to catch a flight back to Houston. I always seem to be waiting around for something. I talked with

my parents and doctors about a port. It sure could make my life a lot easier. I hope you will strongly consider allowing me this opportunity. Thanks for listening. It means so much to me.

**ERIN BULLERS:** As a parent of a patient, who has watched my child struggle with peripheral access, I am especially worried about the physical and emotional toll it will have on Nicholas as he endures 96-weeks of this. Nicholas and other patients in this trial have suffered both physical and psychological trauma due to their participation in the ESSENCE study. And it seems unnecessary if there is another infusion option that exists. As a reminder, the patients in this trial are between the ages of seven and 13. Imagine the seven and eight-year-olds that you treat. How would they react to getting an IV in their arm once a week for two years?

We, and other families in the trial, understand that a third of the patients will be receiving saline as opposed to drug. They will receive saline as opposed to drug regardless of whether or not it goes in through a port in their chest or an IV that took multiple sticks to place. We also understand the risks associated with port placement surgery. But our family believes that the risk of putting Nicholas through continued episodes, like you saw in the video, and the risk of being potentially excluded from the study due to lack of peripheral access and therefore no longer having the opportunity to participate in the trial, outweighs those risks.

Including the option for ports in the study will not affect those patients who do not absolutely need them. It will never be a decision taken lightly, but a choice to consider only when no option other than exiting the study exists. However, that decision should be made on a case by case basis, by the principal investigator with prior

experience in Duchenne and with ports and who have firsthand knowledge of their care. The decision to place a port, even when a port is related to a clinical trial where there's potential to receive placebo, should be left up to the physician, principal investigator and the family.

Some patients in this trial, possibly even Nicholas and Dawson, pictured here, without the option to infuse through a port, may not be able to remain in the study. And that would be devastating for them and their families. In this trial, children are being asked to carry an incredibly heavy burden for the sake of science and innovation. As their parents, I hope you will help us reduce that burden on Nicholas and those who are negatively affected by the ESSENCE protocol by modifying the protocol to include the option to infuse via ports.

Thank you, Dr. Nelson and the Office of Pediatric Therapeutics for allowing our voice to be heard and for taking our perspective into consideration. We are available to answer questions from the panel for the remaining five minutes.

**DR. HUDAK:** First, I think everybody on the committee would really like to thank you for your presentation. And in particular, Nicholas, applaud you for your courage in participating in this trial which, you know, has the likelihood of helping so many other children like you. And for your courage in coming to talk to this group at a very young age.

I certainly empathize with this as a PTSD. I remember as a young boy getting taken to the doctor's office for yet another shot. I think I must have been about three or four years old. It might be one of the first experiences I remember. Hiding under the doctor's table so they had to come get me to get the shot.

I don't think I would do well with 96-weeks of PIV placement myself, but I'll just make that right up-front admission. We have time for maybe one or two questions. And then are you staying for the afternoon discussions?

**ERIN BULLERS:** We are.

**DR. HUDAK:** So if there are any more questions that people have for you, you'll have a chance to answer them at that time. But if there are one or two questions before the break we can take those. Dr. Cunningham?

**DR. CUNNINGHAM:** Melody Cunningham. I guess I just have one question. As you presented you said it would only be an option if it wasn't -- you know, if it came to the point where peripheral IVs were very, very difficult. I guess I'd love your parent, and Nicholas your, perspective on us considering whether it ought to be an option to be placed initially at the start of a trial because you may know your experience with needles in the past.

**NICHOLAS BULLERS:** Yes. It would be a lot better to have the port in with my biopsy.

**ERIN BULLERS:** Yes. I think that would have been helpful at the beginning so we wouldn't have had to go through what we've been through. I mean, it was pretty simple the first month after he started the infusions. But things became very difficult and are still headed that direction. You know, now we're just -- our only option would be to have a port placed. And he will be coming up for his 48-week muscle biopsy in August, so that could also be an option to minimize the sedation risk.

**DR. HUDAK:** Okay. You have another comment? Sure.

**NICHOLAS BULLERS:** Well, getting one poke at the port beats having

to get five in the arm.

**BRETT BULLERS:** He said knowing the fact that you're getting one, you're always getting one. It's just psychologically knowing I'm going to get one versus I don't know how many I'm going to get today.

**DR. HUDAK:** Dr. Fost? Yes?

**DR. FOST:** You obviously go through a lot of challenges to get Nicholas to -- I mean the traveling involved. There have been families that have traveled outside this country to get access to experimental therapies because of inability to get them in the US. Are you aware from your network of any families that have gone to Europe just over this issue? That is to get port access for this sort of trial?

**ERIN BULLERS:** Well, no. There actually haven't been any other trials with Duchenne with the 96-week placebo. It wasn't, you know, something they had to consider. Because they knew that their child could get a port during the weekly infusions for Eteplirsen.

**DR. HUDAK:** Okay. Thank you, again. We will break. We'll extend the break time a little bit to 10 after 11 and re-group for the public hearings. Dr. Nelson? You're looking askance.

**DR. NELSON:** Well, I guess we'll just make -- I mean, are we allowed to do that Marieann? I mean, I thought we were supposed to start at 11:00.

**MS. BRILL:** Yes. We can do that.

**DR. NELSON:** We can do that? Okay. We will do that.

**DR. HUDAK:** Good. Okay. Thanks.

[Break]



## OPEN PUBLIC HEARING

**DR. HUDAK:** So, just some preliminary instructions for all the folks who will be speaking. I understand that there have been speakers who have registered. You each have a number so you'll have some idea of the order that you're in. And I'll try to remember to keep track of the numbers going forward.

As you come forward, for the record, please state your name and your affiliation if that's relevant for the purposes of this meeting. The FDA believes that the Agency and public do benefit from a transparent process that helps insure that all the decisions made by FDA are well informed by the advice and information it receives from its advisory committees.

If you have any financial details relevant to these proceedings to disclose, please do that. Financial interests may include such things as a company or a group's payment of your travel or other expenses. Grant money that your organization receives from the sponsor or competitive sponsor. If you do not have any such interests, you may wish to also state that for the record. If you prefer not to address financial interests, you may still give your comments.

The procedure will be here, we will call people in the order in which we have assigned the numbers. You'll come up to the microphone here and you'll have five minutes to give your presentation. Marieann here is going to work this complicated box. It's a timer. And they'll be a hook that comes out after five minutes and remove you from the speaking arena. They're pretty strict about this. We have to be on time for lunch break at 12:30 because some of the people here have tight travel connections.

I'll start with calling the first speaker. I'm not doing very well on name pronunciation today, you'll have to bear with me. The first speaker is registered Megan Polanin. Is that correct?

**DR. POLANIN:** Polanin.

**DR. HUDAK:** Polanin. All right, I'm sorry.

**DR. POLANIN:** Thank you.

**DR. HUDAK:** Megan, go ahead.

**DR. POLANIN:** Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I am a Senior Fellow at the National Center for Health Research. Our research center analyzes scientific and medical data and provides objective health information to patients, providers and policymakers. We do not accept funding from industry, so I have no conflicts of interest.

We strongly support a drug-regulatory process that ensures that patients benefit from safe and effective new treatments as soon as possible. Patients with Duchenne muscular dystrophy urgently needs such treatments. In order to improve quality of life and save lives, we need empirical data derived from sound science.

That is why we must conduct high-quality clinical trials comparing new treatments with a control group in a rigorously designed, double-blind, placebo-controlled, randomized trial. Even for devastating diseases there is still a placebo effect, which is why a well-controlled clinical trial is so important.

We agree with the FDA's recommendation of a study that is 18 months to 2 years in length, which is essential to establish if there are significant benefits for either of these new drugs. Because this is a longer study, we believe the option of a port-a-cath

may be necessary to ensure that as many patients as possible stay in the study long enough to determine the efficacy and safety of the drugs.

We know there are concerns that one third of participants will not receive a potentially beneficial treatment until after the initial 96-week period. And that some of those patients will be exposed to the risks of a central venous access device. There are two reasons why this isn't as unfair as it seems.

One; there is clear evidence of a substantial placebo effect for evasive procedures in medicine. For example, the nationally respected cardiologist, Dr. Rita Redberg, concluded that even sham surgeries -- surgeries that are conducted as a control group in a clinical trial -- have astonishingly high benefits for patients with heart disease and other very serious diseases, in some cases equal to the benefits of patients undergoing the real surgery. Her article was published in the New England Journal of Medicine.

Given that a port-a-cath placement would require a surgical procedure, it could have a similar benefit even when the treatment medication is not involved.

Two; we don't yet know whether the drugs in the study are beneficial or not. In fact, it is possible that the control group will do as well or even better than the experimental group. This is the purpose of a clinical trial, to determine what works and for whom, in order to benefit a much larger group of patients after the study is completed.

Following the first 96 weeks of the study, the control group patients will have free access to SRP-4045 or SRP-4053 for the open-label 96-week extension if they want it. This free access is a potential benefit that only patients in clinical trials can

expect to have.

Given the need for safe and effective treatments for Duchenne muscular dystrophy, and the methodological rigor of the study, we believe that there are circumstances in which an indwelling central venous access device should be allowed in this clinical trial. In this case, this would occur when IV utilization is no longer viable as outlined in the review. Otherwise, we risk losing patients who have invested in the trial, which has potential benefits for themselves and others.

Patients and their families are the ultimate decision makers regarding participation in this clinical trial. Clear and understandable, informed parental consent and patient assent is critical. The implantation and maintenance of a central venous access device must be clearly spelled out so that parents, caregivers and patients accurately understand risks.

In addition, the stress and pain of failed peripheral intravenous access should be discussed with patients and families and compared to the risks of using a central venous access device. Further, the consent and assent forms must be explicit that there is a one third chance that they will not be receiving the drug for the initial 96 weeks of the study. And thus, experiencing risks without experiencing potential immediate benefit if the experimental treatment works.

As I stated earlier, these participants will likely have the benefit of a placebo effect. Patients with Duchenne muscular dystrophy and their love ones deserve the benefits of the most rigorous research available. At the same time, investing in a clinical trial requires significant time and effort and patients always face risks without any guarantee of benefit.

Patients and families who are willing to participate in a clinical trial, that has the potential to benefit many, should be fully informed about the potential risks and benefits of their participation in order to make a decision that is best for them.

Thank you for the opportunity to comment today and for consideration of our views.

**DR. HUDAK:** Thank you. You were exactly at 5.00 minutes. Our second speaker, Ms. Delanna Thomas and her son Dawson.

**MS. THOMAS:** Good morning. My name's Delanna Thomas. I'm from Midland, Texas and this is my son Dawson Thomas.

**DAWSON THOMAS:** Hi.

**MS. THOMAS:** He's 14 years old and a patient in the ESSENCE Trial, and receives weekly infusions at the UCLA Medical Center. I really appreciate the opportunity to come today and share our experience with you. And our perspective on the ethics of allowing a port in a placebo-controlled trial.

In 2007, my son was diagnosed with Duchenne muscular dystrophy and the doctor who made that diagnosis told us there was no cure for this disorder. There wouldn't be one in his lifetime and we should just take him home and love him as long as we could. That was not acceptable to us. We began the search for every possible treatment.

Then we heard about exon skipping. Not a cure, but a means to dramatically slow the progression of our son's fatal condition. We jumped at the chance to participate in ESSENCE trial for SRP-53, despite the extensive weekly travel and the burdensome protocol which included two open muscle biopsies and a 96-week placebo.

We've always been extremely honest with Dawson about his condition and the challenges that he will face. The decision to participate in the trial was his. He made this decision knowing that his participation would be a major disruption in his life. And that there was a one in three chance that he'd be receiving a placebo. Yet still, he volunteered.

At UCLA Medical Center, we met Dr. Shieh, the principal investigator, who informed us that a port was not approved for the study protocol, and how he hoped that would change in the future. We were not concerned. Dawson has great veins and has never had any difficulty receiving IVs in the past.

After 24 weeks, this is proven to not be true anymore. The same nurses who in the beginning of the trial could get the IV started on their first attempt, are now having to stick my son as many as five times every week. If peripheral IV placement is this difficult at week 24, I can only imagine how horrific it's going to be at week 48, much less week 96.

Our family believes in the ESSENCE Trial. We firmly believe that Dawson's participation is in his best interest and will benefit many other children like him. Why must he endure unnecessary pain? I want my son to live as long as possible and right now this drug seems to be his best hope.

However, the quality of his life is suffering as infusions are becoming increasingly difficult and Dawson's anxiety level is rising. As I'm sure you know, many of the boys with DMD have OCD and sensory integration issues. This means that once the fear of pain sets in, it's almost impossible for him to relax. And any pain he does experience is amplified.

It's not just the initial stick that hurts so much, it's the digging into his arm. I don't want to bury my son, but I don't want to fill his short life with pain and anxiety either.

This is a question of medical ethics. I urge you to consider the ethics from the perspective of the patient. My child is enduring painful, unpleasant procedures which potentially have no therapeutic benefit at all. The pain serves no medical purpose and is completely unnecessary. It's unethical, in fact, cruel to put these children through this torture.

We understand the risks as well as the benefits of the ports. Our family and Dr. Shieh are in the best position to decide what is in Dawson's best interest. I implore you to make your recommendation to the FDA that the study protocol be modified to include the option to have infusions administered through ports when the principal investigator and their family determine it to be in the patient's best interest.

It shouldn't matter whether it's saline or drug. These boys receive the same stick, the same trauma to their veins. How can this study be successful if access to the veins becomes increasingly difficult to the point of becoming impossible? How many of the estimated 100 ESSENCE patients will be able to tolerate it for the entire 96 weeks?

These boys are doing something important, and noble, and good, and they're suffering needless pain. You can do something about that, so, why wouldn't you? Thank you very much for your attention.

**DR. HUDAK:** Thank you Ms. Thomas. And thanks, Dawson, for supporting your mother through that. Our third speaker is Anita Bullers who is Nicholas' grandmother?

**MS. BULLERS:** Yes.

**DR. HUDAK:** Thank you.

**MS. BULLERS:** I can't remember exactly what I'm supposed to say, but I was not paid by anybody. No financial interest. Just did it on my own. My name is Anita Bullers and I'm Nicholas Bullers' grandmother. I live about 30 minutes from Nicholas in Houston, Texas and I have been involved in his daily care since he was born 14 years ago.

As a grandmother of a boy with Duchenne, your heart breaks for your son and also your grandson. I often travel from Houston to Los Angeles with Nicholas for his weekly infusions at the University of California Los Angeles Medical Center. Thank you for providing my family and me with an opportunity to share our experiences with the Sarepta's Clinical Trial of 45 and 53 called ESSENCE.

I heard about exon skipping at Parent Project Muscular Dystrophy annual conference several years ago. Knowing Duchenne was a progressive disease, I was curious how some of the boys were walking further and had more energy than the year before. I learned they were on Sarepta's Eteplirsen Trial.

Upon further investigation, I learned that Sarepta's next exon skipping trial would be amenable to patient who needed exon 45 and 53. Nicholas needed 53. As you know, the 96-week ESSENCE Trial was delayed a year. When the trial started enrolling, not only did the age range change from 7 to 16, but it decreased from 7 to 13, and the length of the placebo was extended to 96 weeks.

As you might imagine when the age of inclusion was decreased to 13 years, we were in a panic. Nicholas was 13. He could no longer get off the floor and he was

walking shorter distances. We were worried that he might lose this opportunity.

I was surprised to learn that the ESSENCE protocol did not allow for ports. Initially, I wasn't concerned since Nicholas was familiar with having blood draws. His veins cooperated and he handled needles quite well. His nurses were able to access his veins with one, maybe two, sticks. However, that is no longer the case.

Last week, when I took him for infusion, Nicholas had three nurses working on him for two and a half hours. Sticking him four times. When they start fishing for a vein and he's begging them to stop, as you saw in that video, it's heartbreaking and, in my opinion, unethical to put a child and his family through this week after week.

I assumed if his medical team deemed it medically necessary, he would be allowed a port. I had no idea this was not an option. Despite my misgivings about the trial design, we know that the clinical trial is the fastest way possible for Nicholas to gain access to a drug we believe will benefit him.

Nicholas' parents, clinicians and I try to reduce the number of sticks and anxiety associated with infusions. The nurses use a vein finder to locate Nicholas' veins. Unfortunately, Nicholas' veins are deep and they have extensive scar tissue. The device has not been helpful. We hydrate Nicholas the night before and the day of infusion. We fly into Los Angeles earlier than necessary and we give him the best shot at being rested and hopefully have a good day. Nicholas uses deep breathing meditation techniques. Sometimes they work, but not always.

We are acutely aware of the risk of the port placement surgery. Be assured, nobody takes these risks lightly. Our family believes, that for Nicholas, infusions

through a port-a-cath would be a substantial improvement in his quality of life and trial experience.

We believe there is a greater risk to his mental and physical health if he continues with the peripheral vein access. More importantly, it would be devastating if Nicholas could not continue in the ESSENCE trial.

I know these are questions you are thinking about as well. I look forward to hearing how we can mitigate issues in clinical trials like the one we're discussing today. Thank you.

**DR. HUDAK:** Thank you very much. Our fourth speaker is Christine McSherry. Welcome.

**MS. MCSHERRY:** Good morning. My name is Christine McSherry and I'm here today to talk to you wearing three different hats. The first and the most important is I'm a mom. I'm a mom of a 21-year-old boy, Jett, who has Duchenne muscular dystrophy. He receives weekly infusions of EXONDYS 51. I'm also here as a leader of his advocacy group, the Jett Foundation. And lastly, as a registered nurse who has experience with peripheral IVs and port-a-caths for patients who receive frequent infusions.

Let me start by saying that I can't even imagine what these children and these parents are going through. The stories that you have heard, and will hear, are appalling in nature to me as a mom and as a nurse. As a mother of a son who has weekly infusions of a drug, I can tell you with the utmost certainty that we, like others, weighed the risks and benefit of surgery of having that port placed.

My now 21-year-old son, Jett, like many affected by Duchenne, was a

victim of poor peripheral access. And as a nurse, I can tell you that I did everything I could to start every IV he needed. I watched him being poked and probed through his early childhood. And as it became more serious when he entered a clinical trial in November of 2014, Jett enrolled in the Eteplirsen number 204 Safety Trial.

At the beginning of the trial he did not have a port. It quickly became obvious, when the expert IV nurses at Mass General Hospital could not access him, that he would need a port or he would be unable to continue in the safety trial.

For the first eight weeks of the trial, the IV nurses accessed him via his foot, his shoulder and his neck. And each time they accessed him, it became more painful, stressful and difficult for Jett. Even at the age of 18, Jett had difficulty managing the pain and the anxiety that came with each peripheral access attempt.

Over the course of those eight weeks, Jett and I made the decision together that a port would be the only option for him to continue in the trial. And we were willing to undergo the procedure to get the port. We felt that there was a minor increase over minimal risk.

At 18, we weighed the very heavy risk associated with the placement of a port against the benefit of receiving a drug that could potentially benefit him by slowing the progression of his Duchenne. Jett underwent surgery in 2015, with a highly-skilled staff that the neurologist and myself worked closed with so that all the risks were understood. We all worked as a team to ensure a successful outcome.

The surgery went well. Jett was in and out of the OR in less than two hours. And I visited up in the PACU, with his Cough Assist in hand, anticipating possible pulmonary issues. But surprisingly enough he didn't need it. He came out of

the anesthesia well and was discharged that day to home.

Within a week of having that surgery, the port was accessed and used for infusion. Since that time, the port had been accessed 88 times during the clinical trial, all usually with one little stick.

Also, during two medical emergencies where Jett was hospitalized for kidney stones, I walked into the ER with my son, was able to access him right away and the nurses were able to use the port. We also use it for routine blood draws; as you can imagine, those too can be traumatizing.

Over the last two and a half years, many nurses, including myself, were able to access his port without difficulty. His anxiety and pain that Jett once experienced during those early infusions is now nonexistent. Accessing Jett, administering his medication is now not a worry. He's worry free and it is just part of his routine.

The risk undertaking a port placement procedure ultimately paid off for our family as it allowed Jett to access a drug that ended up stabilizing his disease.

I hope you can use Jett as a case study and how successful port placement surgeries can improve a clinical trial participant's quality of life. Today you will hear from families grappling with a similar situation as I did with Jett. And as a nonprofit leader who speaks to patients and families every day, I ask that you truly listen in here today and understand that we advocate for this to be a decision by those who are in the trenches, the families and the doctors who are involved in these studies.

These parents are savvy and they're very smart. These are parents who have done their research and have committed themselves and their kids to the greater

good. Thank you.

**DR. HUDAK:** Thank you very much. Our fifth speaker is Suzanne Gaglianone.

**MS. GAGLIANONE:** Pretty good. Not bad. Good morning. I appreciate the opportunity to tell my family's story. My name is Suzanne Gaglianone and I have no conflicts. I'm here with my 21-year-old son, Michael, who has Duchenne muscular dystrophy.

Michael is participating in the Sarepta study in non-ambulatory patients, skipping exon 45. He had his week 77 infusion on Tuesday. Every week since December 2, 2016, we have travelled from New Jersey to Maryland so that he can receive the infusion.

The opportunity to participate in a trial was something we had worked for, hoped for and prayed for for over 14 years. We knew that his participation in the study could be what changed the progression of the disease and potentially our last chance at a trial.

Our study allows the participant, the parents and the PI to decide if a port is appropriate. Michael was 20 years old when we entered the trial. I was very leery about him going through this procedure. I gathered information about port placement, ports in general. I gathered the pros and the cons. I asked parents enrolled in similar studies what their experiences were with and without a port.

We were already all too familiar with the difficulties nurses had been having with peripheral vein access with Michael for years. We had already tried extra hydration, the vein finders, the VAT team, even ultrasound all to no avail. We have

been part of the Duchenne community for a very long time and this is the norm. It's just what the poor kids have to go through.

In the meantime, while we were gathering this information, Michael received his weekly infusions, but he was becoming more and more anxious about the visits. Accessing the veins was becoming more and more difficult. It was multiple sticks. And we really shouldn't minimize the anxiety this causes not only Michael, as the patient, but parents and the nurses.

After careful consideration looking at the potential risk to Michael, with the repeated weekly peripheral vein access, weighing that against the potential therapeutic benefit, we opted for the port. On January 27, 2016, Michael underwent the procedure to place the port.

One of my biggest concerns was the anesthesia and respiratory distress. Even at 20 years old, the anesthesia was noninvasive. They had an ICU bed available for him in case; it was not needed. His recovery was rapid and we were released.

The following week, access was a breeze, but that only lasted for two weeks. After that an x-ray revealed that the line had migrated out of position and it couldn't be used. My initial reaction was that we should not have another port place. How could we expose him to this risk again?

However, Michael wanted to continue in the study. But he also voiced that he did not want to continue with the weekly torture of multiple sticks. I was still unsure. As is usual, no decisions in Duchenne are taken lightly.

Then our week 12 infusion, it took nine sticks to gain access. After eight sticks the nurses said that was enough, but Michael said please just try one more time.

They got it. I want you to understand when I say stick it is not just a needle prick. You witnessed it. It's a fishing expedition. Searching through tissue. They're hoping to find this vein, they're not going to find it. It's torture for everyone.

On March 31, 2016, now over a year ago, Michael underwent a second port placement. We wanted to continue to participate in the trial. And after weighing the pros and cons for a second time, this was our decision. We are so thankful that as a family, along with the PI, we had the opportunity to make this decision.

It was not easy, but next Tuesday we will take our 78th weekly trip for Michael's infusion knowing that he is doing well and knowing that we made the right decision. Thank you for your time.

**DR. HUDAK:** Thank you. Our sixth speaker or speakers --

**MS. MAJORS:** It's just me.

**DR. HUDAK:** Just you. Are you Rebecca?

**MS. MAJORS:** Yes sir.

**DR. HUDAK:** Rebecca Majors. Okay, thanks Rebecca.

**MS. MAJORS:** I'm Rebecca Majors. I am a mother of two boys with Duchenne. One turned eight yesterday and one is five. Thank you for allowing me to speak today. As you are aware, I am here to speak about a change to the protocol for the ESSENCE Trial on behalf of my sons, Nathan and Easton, and all the patients living with Duchenne muscular dystrophy.

To you they may be names in a sea of many patients, but to me they are my world. And unfortunately, for our families, so is Duchenne. I would like to take a moment to share how our family and our 7-year-old son, Nathan, became involved in

## ESSENCE.

It all started a few months ago when we made a small trip from Georgia to Iowa that changed our lives. During this trip, for the first time since our sons were diagnosed, we felt the glorious feeling of hope. Hope isn't something families affected by Duchenne is given very often. Most of the time, we're told just to take time with them, there's no cure.

Now don't get me wrong, we had our reservations about the trial. We knew our lives would change drastically with the weekly flights and infusions. We knew that there may or may not be complications. But what parent, in our situation with children dying of a progressive disease, would not jump on the chance to help find a possible treatment that could slow the course of their disease.

At first, we just assumed that our son would be able to have a port placed as part of the clinical trial. But we were quickly informed that a port would not be an option in ESSENCE. We would have this undeniable faith that told us to keep on going, because ultimately our sons were in the best hands possible. And we believed that this clinical trial was the only opportunity to slow down the disease progression.

We prepared our seven-year-old that during this trial he was going to be getting medicine that was like Captain America's. What seven-year-old wouldn't love that comparison? We told him that we were hoping it would make his muscles grow strong. Nathan was just excited that he could one day be on American Ninja Warrior.

Our son started the trial and we soon discovered his veins were weak and frail from the steroids he takes. And because, like the rest of the tissue in his body, he was missing dystrophin in his veins which made them weak and collapsible, I remember

the feeling of deep sorrow and fear that Nathan wouldn't be able to continue with the trial because the nurses had such a hard time accessing him every week during infusions. But despite the issues, we continued flying to Florida from our home in Georgia for infusions once a week for about two months until our worst nightmare occurred.

This time the nurses were able to access Nathan, but shortly after they got the IV in the vein, the vein blew and the site started to swell. The nurses started another IV in another vein, but that one blew. Next, we tried two more veins and both of these blew.

At this point I'm crying and my son is crying, screaming and shaking. I remember how much my heart hurt that day. It was a feeling of helplessness that no parent should ever feel.

We still continued flying to Pensacola for infusions for the next three weeks. But every time the nurse accessed him, his veins blew. At this point we had four to five veins blowing every single week. Imagine the anxiety my seven-year-old feels before every infusion appointment.

Nathan started throwing up the night before because of how nervous he was. And the waterworks started as soon as the nurse, who he actually loved, walked in.

One scene that plays in my head, over and over again, is having to hold my child down as the nurses try to put the fifth IV in that day, only to have it blow seconds later. I could actually feel my son's tears rolling down on my hands.

After a few weeks of this, the clinic put my son Nathan on a clinical hold and asked that we only come in for weight checks. I just still have the feeling of despair and just this uncertain notion that without the port he won't be in the trial, simply

because his veins aren't accessible and the protocol won't allow him to be infused through a port.

It was devastating because we know, and his doctors know, if Nathan has a port, that he could be back in the trial. As a parent of a child with a deadly illness, the worse feeling is to have hope ripped away.

Yes, we understand that Nathan could be getting a placebo for 96 weeks. Yes, we understand that ports are intrusive and that a port placement surgery is risky. But in Duchenne there is almost nothing riskier than doing nothing. In Duchenne, a progressive disease that can eventually lead to death, there is nothing riskier than not trying everything possible to save their lives.

Today I'm asking you to recommend that the FDA change its protocol to allow patients to be infused via port when the access becomes difficult or nearly impossible. I'm asking you to please allow the principal investigator and the parents to weigh the risks and benefits of port placement surgery and make a medical decision that is best for the patients.

If this change is not made, my son will never be able to continue in the trial and time is short. Thank you once again for your time and listening to my perspective.

**DR. HUDAK:** Thank you. Our seventh speaker is Jenn McNary.

**MS. MCNARY:** Good morning. Listening to these testimonies I'm having a little PTSD myself. My oldest son and younger son both have Duchenne muscular dystrophy. And my younger son, Max, was in the Sarepta's trial for EXONDYS 51. He was a difficult peripheral stick; in fact, he mirrored the video you saw earlier. He had veins that were blowing. He had multiple attempts before access

was finally obtained.

We had a very similar story about 20 months into the trial. Finding a vein that wouldn't burst or collapse became impossible. His last infusion at Dartmouth-Hitchcock Medical Center, before his port placement, took 12 attempts and six nurses; because in certain hospitals, each nurse is only allowed two attempts. It was finally a NICU nurse who succeeded in the top of his foot.

Max was hysterical when he came home. The trial coordinator called me later that day and informed me that they would no longer be willing to keep infusing Max for a clinical trial unless he had a port-a-cath placed. We were able to scramble, and because we were allowed, in that trial, to have a port, he didn't miss a single dose. He's now had his port-a-cath for three and a half years.

He has not had a single complication from neither the surgery or the port-a-cath. Each week, during his now home infusions, on approved drug, it takes one try to access; it's painless. He does it while playing a computer game. It's done without anxiety. I'm often not even home. It's done by one home health nurse.

The trial drug is now approved, largely, on the data that Max was able to provide as one of the 12 children in this clinical study. He was providing data collected, during a muscle biopsy, that he would not have been able to have if he didn't have his port-a-cath. It was used to give him the medications that sedated him.

The larger issue here is that the Duchenne population is so small, as in other rare diseases, that in order to power the study, the company had to wrap two drugs into one trial. If we lose participants now, in this study, we run the risk of not having studies for Duchenne at all.

I want to suggest that the patients that you've heard from today in the room, and the other ones that will be coming forward needing a port-a-cath, be given the same opportunity that my sons have been given to have an anxiety-free trial experience, and the ability to complete their clinical trial. Thank you very much.

**DR. HUDAK:** Thank you so much. Our eighth speaker is Brian Denger. Welcome.

**MR. DENGGER:** Thank you. My name is Brian Denger, and I speak on my family's behalf. I live in Biddeford, Maine, with my wife and son who has Duchenne muscular dystrophy. I appreciate this opportunity to speak to the committee about amending the trial design of a clinical investigation that involves children and FDA regulated products.

My comments concern Sarepta Therapeutics ESSENCE clinical trial, for two exon skipping drugs, to treat Duchenne muscular dystrophy patients with specific amenable genetic mutations. This clinical trial requires weekly IV infusions of both investigational drug and placebo over 96 weeks. I urge the committee to allow the option for any and all study participants to consider the use of a port-a-cath, a central venous catheter or IV line; meaning the catheter is threaded into one of the large central veins in the chest, which empties into the heart.

While the port provides relatively easy access, I understand it also carries greater risks. As the father of two young men affected by Duchenne, I have carefully and thoughtfully weighed the benefit and risk of such a decision.

As background, I have been involved in the Duchenne community for over 20 years. My son, Matthew, deceased, was diagnosed in 1997. His brother, Patrick, is

22 and will graduate college Saturday. From the time of diagnosis, my sons were regularly subjected to blood draws as part of their clinical assessments. As little boys, they quietly accepted each draw and rarely flinched.

In time, as muscle tone diminished and contracture hindered access, the ability to find and access a vein became more difficult. Single sticks became a thing of the past. A second nurse would be called in and sometimes the lab would call a member of the IV team. Matthew and Patrick didn't complain, yet the effects of multiple sticks were obvious. The procedure is painful, especially when repeated over time, and each draw took longer.

As appropriate Duchenne clinical investigations became available, my sons enrolled. Each study required blood work for relevant labs. The experiences were the same. My sons tolerated being subjected to several attempts to access a vein. They tried to drink plenty of water beforehand and were given warm towels; yet, low muscle tone and small veins weren't much help.

Watching nurses pat my sons' hands, search their arms and hands for an accessible vein wasn't easy. Even worse, was watching them insert a needle in their wrist, in the back of a hand or lower arm where a viable vein was seen. It became progressively more difficult over time, often leaving them with bruising and soreness at the access point.

My sons' experiences are common for a person with Duchenne. Patrick recently completed a clinical trial in which he had blood draws almost every other week over a seven-month period. Convincing him to allow one more attempt, after seven or more failures, tested us both. True, he was an adult. The reality is, these challenges

began when he was a child.

The accumulative effect of these multiple draws cannot be overstated. Multiple blood draws for laboratory assessments and IV infusions are necessary for those participating in specific clinical investigations.

For an adult, the choice to participate in a trial should be made autonomously. A child is at the mercy, though, of their parents who choose on his or her behalf. Participation in a clinical trial places enormous burden on participant and family. Ninety six weeks of IV infusions, regardless of what is administered, compounds the effect.

These frustrating experiences leave a long lasting psychological impact on parent and child. Today's meeting is to consider allowing participants in the ESSENCE trial to use a port-a-cath where there is a possibility they may receive placebo. While weekly IV infusions are allowed for those receiving placebo, it is argued the use of a port conflicts with regulation.

Yet children and adults with Duchenne seen in the interest of clinics, undergo periodic blood draws and may require IV. Not all will use a port, yet some do.

There is little question that there are risks to a port, possibly serious. Providing study participants an option to weekly sticks is not about convenience, it is lessening the physical and psychological trauma faced with weekly IVs.

It is difficult enough to ask families and children to participate in a study, of an investigational drug that may slow the progression of Duchenne, when there is a likelihood of receiving placebo; especially as participants are at the age where they will soon lose the ability to walk. Knowing the challenges of typical, less frequent blood

draws and IVs, tells me the study is designed with weekly infusions as significantly more burden. The decision isn't about expediency, it's about compassion and empowering families and children with options. It's a sensible approach to the advancement of science.

**DR. HUDAK:** Thank you, Mr. Denger. Our ninth speaker is Erin Bullers. Thank you. I got it right this time.

**MS. BULLERS:** Yes, you got it right this time. You get to hear from me again. My name is Erin Bullers. I'm Nicholas' mom and we're from Houston, Texas. I spoke with you earlier in the parent and patient presentation. While I provided you with my prospective on peripheral access issues in the ESSENCE study, I thought it would be important to talk about our participation in this trial.

Our decision to enroll Nicholas in this trial was a no brainer. It was a chance to get him access to a drug that could slow the progression of Duchenne at his age of 13. At the time, we did not consider the burdens participation would bring.

It means one or two nights a week, I'm away from my husband and my 11-year-old daughter, loss of time with extended family. Nicholas has missed time spent with friends, family vacations, and will even have to miss going to MDA camp this year, his favorite week of the year.

He spends two hours in the car, every week, traveling to and from the airport; three-and-a-half-hour plane ride from Houston to Los Angeles. Transfers in and out of cars and airplanes. In addition to the weekly infusions at the University of California Los Angeles Medical Center, we travel to Cincinnati Children's Hospital every six months, where Nicholas has been seeing his specialist since he was 4 years

old.

Nicholas is required to perform 20 outcome measures for the ESSENCE trial every 12 weeks. After he's faced with repeated attempts to access his veins, followed by a 4-hour infusion, we return home knowing, preparing ourselves for the next week, recognizing that Nicholas may be receiving placebo and not active drug.

We are here today because it matters. It matters for Nicholas, for me, for his father and for his grandmother. It matters that Nicholas has options. And there is not a day when we're not praying that this drug is an opportunity that will make a difference for him and the other boys who need and deserve options.

Today we are talking about having an option for port placement to reduce the burden of participation. To reduce Nicholas' anxiety, to improve his access, to ensure he is able to complete the study and have access to a drug.

Today I ask you to thoughtfully consider this important decision. As you might imagine, there are many issues to consider. Thank you, Dr. Nelson, for bringing this critical decision to this committee. My family and so many others appreciate this opportunity.

**DR. HUDAK:** Thank you again. Our tenth speaker is Jordan McSherry and she will speak on behalf of Leslie Guzman (phonetic) and her son, Diego (phonetic).

**MS. MCSHERRY:** I'm speaking today on behalf of Leslie Guzman, the mom of a little boy named Diego who was supposed to attend today's meeting. Diego is a 12-year-old in the ESSENCE study who struggles with peripheral access issues. He broke his hip last week in a fall, underwent surgery on Friday and could not attend.

Diego has been participating in the ESSENCE trial since March, 2017.

Since Diego began receiving weekly infusions, the nurses at Nationwide Children's Hospital has been having an increasingly difficult time accessing his veins. You see, not only does Diego have Duchenne and has veins without dystrophin and muscle tone, he was also born prematurely and spent three months being repeatedly accessed in the NICU.

Since then, many of the veins in his body remain inaccessible and he has serious difficulties being accessed peripherally. Having bloodwork drawn is so bad for Diego that we've actually suffered more from the repeated blood draws and IVs than from Duchenne itself. It is very common for him to suffer several pokes and failed attempts every time he needs bloodwork or an IV, despite the extra care from the hospital's team.

I know that as the trial continues, this issue will get worse, not better. It causes Diego undue suffering to continue this way when other options, such as port-a-caths, are available. The problem worsens when Diego experiences medical emergencies like surgeries or heart MRIs. When Diego broke his hip last week, and needed surgery, the doctors were in the impossible position of having almost no peripheral access and no way to administer pain medication.

We ended up waiting two hours for an expert IV team to arrive with the equipment and expertise needed to access someone like Diego. It is a beyond heartbreaking revelation for our family that something completely beyond Diego's control will likely prevent him from continuing to participate in the ESSENCE trial. His veins are going to get in the way of his participation in a groundbreaking study that is a potential to slow the progression of this disease.

I need help from this panel, and from the Office of Pediatric Therapeutics, to provide my son with the opportunity to continue with ESSENCE. I need you to recommend that the study protocol be modified so that kids who need a port for the duration of the ESSENCE study can get one. I believe that the benefits of infusing Diego through a port outweigh the risks because this trial and the drug being studied has the potential to slow his decline. And without a port, Diego's veins will continue to be destroyed and his life can be put at risk in a future medical emergency.

Please recommend to the Commissioner that ports be allowed in this study for the sake of my son and others like him. Thank you very much for listening.

**DR. HUDAK:** Thank you very much. Our eleventh speaker is Shelly Mays.

**MS. MAYS:** Hi. I have no financial interest. Good morning. My name is Shelly Mays and I'm a senior research coordinator in Hematology/Oncology at Children's Healthcare of Atlanta. I also happen to be the aunt of Nathan and Easton Majors, both of whom have Duchenne muscular dystrophy.

While my expertise is not DMD specific, CHOA is a site for several trials that require frequent infusions in order to participate.

Today, I come before you as a family member, and also as a coordinator that troubleshoots and navigates the complexities of clinical trials as my profession. Arguably, one of the most critical components of all clinical research is the informed consent process. That is an opportunity for discussion about the study, the patient's and family's rights as participants, potential risks and benefits and various optional components. All consent forms are reviewed by an IRB before any consent discussion

should occur.

Typically, it's the local IRB that assesses the risk/benefit ratio. Those studies which are considered higher risk may require things like both parents' signatures. It is during this process that risk for port placement should be discussed. It should be an optional component, which local IRBs decide if that option is of an acceptable risk/benefit ratio to offer for their patients.

I am sure that recruitment for this trial has got to be somewhat difficult. This medication is exon deletion specific, which makes it even rare within the diagnosis of DMD. Having a weekly infusion requires a lot of time off from work and school. There is also the required need for access to run the infusion with patients who take a steroid that makes their venous access worse.

The families that have agreed to take part in this trial are committed to finding some sort of treatment for their children. The potential of receiving placebo puts their boys in no more harm's way than the alternative, which is no treatment whatsoever. They carefully consider and weigh both physical and psychological risks to their child. If a family decides that they are willing to risk exposure to anesthesia and surgery, to save that child from trauma of weekly, multiple sticks, it should be an opportunity afforded to them.

It has also been my experience that patients, who have been on our clinical trials, receive a benefit from being on a clinical trial. The visit frequency is greater and so they are more closely monitored with complications that would come from the medication or from their disease process.

As a part of a multidisciplinary team, we're able to keep close tabs on the

whole patient and family. We get to know them much better and their disease, as well as social, psychological and financial concerns that affect the family. This added benefit is afforded to both the treatment and placebo group. You get to know your families well when they are doing a trial because you spend a lot of time with them, communicating with them and reviewing their condition.

Another substantial consideration is that there will be an open-label offering of this medication after the placebo timeframe is completed. Even the children that initially would be on placebo will have the option to take the open-label drug, once they've completed their initial treatment.

If this medication can only be given weekly, via infusion, it would be a disservice to these children to not have an opportunity for port placement. Several children, at our facility, have ports placed for less frequent need for access via central or port.

Though I do recognize that exposure to anesthesia and port placement surgery does come with more than minimal risk to the patient, the benefits of participating on a clinical trial afford an opportunity for treatment, either initially or on open-label phase for a devastating disease in which there is no treatment. They would be closely monitored for any possibly complications from the port placement; not to mention saved from the physical and psychological trauma of multiple sticks to get venous access.

While I do not think that port placement should be mandatory for participation, I think the best option to have one placed would be in the best interest of the child, given the frequent visits and length of the trial. I hope that you give some

thought to my remarks and consider letting local IRBs decide what is or is not an appropriate offering for their patients. Thank you for your time.

**DR. HUDAK:** Thank you, Shelly. Our twelfth and final registered speaker for the day is Neera Gulati.

**DR. GULATI:** I'm representing Suneel's Light from Buffalo, New York. My name is Neera Gulati and I'm a family physician and Suneel Ram's mom. My son, Suneel, is 20 years old and has Duchenne. For over 16 years, I've been traveling and meeting with DMD clinicians, scientists and families in many different countries. Suneel's Light is a nonprofit organization dedicated to spreading awareness about DMD and raising funds for research. Our efforts have helped fund exon skipping research as well as other potential treatments for DMD.

Because dystrophin is absent in Duchenne, dystrophic veins and muscles make peripheral IV access very difficult, and in many cases impossible due to the pathophysiology of the disease. It is paramount to leave the decision for central venous access port-a-cath placement to patients and their physicians. Having no option for central venous access makes it impossible to complete clinical trials according to the current requirements.

Restricting access to central venous placement paralyzes completion of the trial. The only reasonable and ethical choice here, is the decision should be given to the clinicians and the patients who are dealing with this disease every day.

**DR. HUDAK:** Thank you very much. At this time, I'd like to just survey the audience and see if there are any other people who haven't registered, who wish to speak.

**DR. DRACKER:** My name is Dr. Bob Dracker. I am a hematologist pediatrician, obviously, an infusion therapy specialist. I've had the pleasure of taking care of two boys in the trial for over five years that are twins. For about a year and a half I struggled with them to gain IV access and finally put a port in both of them.

The reason I wanted to speak was to give a broader prospective to the subject matter. When we diagnose a child with a malignancy, part of their initial therapy, usually within the first 48 hours, is the placement of a port, really to make their lives easy and always have access for the therapy.

In my infusion office, I see probably between two and three hundred patients a week. Many of whom, if they receive therapy on a weekly or biweekly basis, we put ports in, just to make their lives easier.

I think the broader subject matter to consider is that there's obviously a deficiency in pediatric trials. And some of these trials, access and continued therapy is done sometimes on a very frequent basis, even more frequent than every week.

Part of the issues to consider is that to facilitate the effectiveness of a trial and importance of a trial, I think in the future the issue of intravenous access should be considered. Such that maybe the placement of alternative devices such as ports should be considered at the forefront, really to minimize the trauma to the child and to increase the effectiveness of the study. Thank you.

**DR. HUDAK:** Thank you, Dr. Dracker. At this time I'll conclude the public hearing by reading into the record three comments that were received in written form in advance of the meeting from folks who could not be here.

The first comment is from a Dr. Norbert Weidner from Cincinnati

Children's, talking about the risk of anesthesia in boys with DMD.

Dr. Weidner recommends that placement of an indwelling port be done in a full-service hospital with an anesthesia team that has experience with DMD patients. He also notes that for patients on chronic steroid treatment, coverage with steroids during the period of surgery needs to be considered. He included an attachment with published recommendations on the surgical and anesthetic care of patients with DMD, but did not provide the source. The following paragraph is illustrative of his comments.

Because individuals with DMD are at risk for hyperventilation and apnea, care must be taken when considering narcotic analgesia/procedural sedation. Existing guidelines call for using assisted ventilation in selected individuals during the induction, maintenance and recovery from sedation and anesthesia.

Succinyl choline is contraindicated because of the potential for rhabdomyolysis and fatal hyperkalemia. Although not generally applicable to care in the emergency department when anesthesia is necessary, a total intravenous technique should be used with strict avoidance of inhalational anesthetics that may cause acute rhabdomyolysis and hyperkalemia when possible use of local anesthesia is advisable.

Second comment is from Ronald Litman, from the Children's Hospital of Philadelphia, submitting on behalf of the Parent Project Muscular Dystrophy.

Dr. Litman supports inclusion of implantable ports for use in DMD patients in the ESSENCE study. He stated the following:

"I believe that it is ethical for each family to make its own decision about the appropriateness of port placement with full knowledge that their child may be assigned to the control group for as long as two years. This decision should, of course,

be made in concert with the treating physician as well as the anesthesiologist and surgeon responsible for the placement and maintenance of the port. These individuals would describe the risks and benefits, as they are different for each child based on the child's comorbidities at the time of the port placement procedure.

I also recommend that each treatment center establish a plan to monitor the risk of port placement so as to periodically reassess the risks/benefit ratio. This monitoring may influence that ratio in subsequent children that participate in the trial, and should be reported to the company and the FDA.”

A third, and last, comment was submitted by the Jett Foundation, detailing the difficulties that DMD patients have with peripheral venous access in the ESSENCE trial. They note that these children may be faced with being removed from the study because the use of the ports is not allowed.

“The decision that a port infusion in this study is unethical, and puts the child at a higher risk than repeated venous access attempts, should be left to the principal investigator and the physician that sees the individual patients weekly and best understands their experience.

The Agency, nor the Pediatric Committee, and the Pediatric Ethics Subcommittee, can make one overarching decision for all patients in the study without having any knowledge of what each weekly peripheral access episode is like for them. It is only appropriate that the principal investigator use his or her extensive knowledge, of the patient's medical history and experience, to work with the patient and the parents to decide whether or not a port is necessary.

That concludes our period of public comment. We have finished a little

ahead of time. It is 12:10, so for those who need to be back in the room for the start of the afternoon session, we'll make that at 1:10. Until then, thank you.

**[BREAK FOR LUNCH]**

## SPONSOR PRESENTATION

**DR. HUDAK:** We are ready to get started for the afternoon session. With everybody's fingers crossed that this all works for one more slide presentation. We start off this afternoon by sponsored presentation from Genevieve Laforet, who's the Medical Director of Sarepta Therapeutics. You're on.

**DR. LAFORET:** Thank you very much. Good afternoon everyone, I'm Genevieve Laforet. I'm the medical director for the Sarepta study, ESSENCE, that we are talking about today. And on behalf of Sarepta and the whole ESSENCE team, I'd really like to thank FDA, Dr. Nelson, everyone here for the opportunity to speak with you and take part in today's advisory committee meeting.

During my presentation, I'll first review, very briefly, the regulatory history that led to today's meeting. And then provide a brief overview of Duchenne and the investigational products being studied in the ESSENCE trial. And then a quick review of the ESSENCE trial design.

I'll next turn to the Sarepta experience with ports in our DMD trials, and the impact of precluding ports in ESSENCE, both on patients, as we've heard about today, as well and on the trial, itself. And finally, I'll outline a proposal for protocol language that would permit port use in ESSENCE with some important provisos.

Let me first start with a few introductory points to set the stage. As you know, ESSENCE is a phase 3 placebo-controlled safety and efficacy study of SRP-4045 and SRP-4053 in pediatric DMD patients. This study includes approximately 2-year placebo-controlled period. And that's really the crux of the matter. Ports have been used

in other Sarepta DMD studies, but none has had such a long placebo controlled period.

And there was central IRB that first raised concerns about the use of ports in ESSENCE, citing greater than minor increase over minimal risk without prospect of direct benefit in placebo patients. Of note, because of the double-blind placebo-control design of the trial, there's no way to allow ports only in active treated patients; because this would require un-blinding their treatment assignment. So from the Sarepta perspective then, this posed a dilemma.

Our previous trial experience suggested to us, that a significant proportion of patients who started treatment without a port ultimately require one in order to complete all of their weekly infusions. So as such, precluding port use in ESSENCE may negatively affect not only the patients participating, but also the conduct of the trial itself. Accordingly, our proposal is to allow optional use of ports as needed at the discretion of the investigator.

Now, this timeline slide is intended to show just a high-level summary of the ethics regulatory history pertaining to ports in ESSENCE. And I won't review this because much of this has been covered in previous presentation. But I really want to highlight and emphasize how collaborative this whole process has been in working with FDA, Dr. Nelson, and his colleagues, pretty much from the get-go. We, as sponsor, are very appreciative of that.

Now, to give a quick overview, this was covered in such great detail by Dr. Shieh this morning, but to hit on a few key points about Duchenne muscular dystrophy. It's the most common muscular dystrophy and it's the most common fatal genetic disorder diagnosed in children. It is truly a rare, or as we call orphan disease affecting

about 1 in 3500 to 5,000 males born worldwide. And it's caused by mutations in the dystrophin gene, the gene that codes for dystrophin protein. And this is the key structural protein that stabilizes muscle fiber membranes.

The most common Duchenne-causing mutations are large out of frame exon deletions in the dystrophin gene. And these kinds of mutations account for approximately 80% of DMD cases and lead to an absence or near absence of dystrophin protein. Clinically, the result of this dystrophin deficiency is a progressive and ultimately fatal muscle wasting disease that has multiple comorbidities. It's important to recognize that besides the effects on muscle strength and mobility, it also is accompanied by compromised cardiac function, compromised respiratory function that worsens over time.

In order to address the considerable unmet medical need for Duchenne therapies, Sarepta is developing investigational products that are designed to allow production of dystrophin via a mechanism known as exon skipping. So as I was saying Dr. Shieh covered this in a lot of detail this morning, so I'll just touch on some of the keypoints now.

As you can see, in the top most diagram under normal conditions, the message that carries the instructions for making dystrophin protein contains all of its components and these components are called exons. And this then allows production of normal full-length dystrophin protein. But in most cases of Duchenne, one or more of these exons is missing, as shown in the second diagram. And as a result, the information downstream of this missing section is shifted such that the instructions for making dystrophin protein become garbled. And the protein that actually gets made is so

abnormal that the body ends up just degrading it, and so resulting in very little to essentially no dystrophin.

As shown in the bottom half of the slide, the whole concept behind exon skipping is to drive removal or skipping of an adjacent exon; so that the downstream instructions are back and register again, and convey the correct information for making dystrophin again.

The intended result is production of a shorter form of dystrophin protein that's missing a section in the middle, but the bulk of the protein on either side is intact. The two investigational products being studied in the ESSENCE trial, SRP-4053 and SRP-4045 are designed to skip exons 53 and 45 respectively.

Just to recap a bit about the design of the ESSENCE trial participants must be patients -- Duchenne patient's aged -- this part I can read while we wait for the graphic because many of you have seen the graphic already -- so they must be 7 to 13 years-old, and who have mutations amenable to either exon 45 or exon 53 skipping.

As described earlier, the first part of ESSENCE consists of a 96-week double-blind placebo controlled period in which patients are randomized on a 2 to 1 ratio to receive either active drug, either SRP 4045 or SRP-4053 depending on their genotype, or a placebo and this is all administered weekly once a week by IV infusion.

The reason for this very lengthy placebo-controlled period is based on our experience with Eteplirsen. In which, especially on 6-minute walk test as a clinical outcome, it took time for dystrophin to be made and for that to translate into a clinical effect. So if you're looking at a clinical endpoint like 6-minute walk test, we know from existing data that it's going to take two years.

One thing that was also raised earlier, there was a question about the blood draws, which could be done through a port in which were not. The concept behind the PK draws not being drawn from the port, is that there's residual drug. But the schedule for PK assessments is every 8 weeks for the first 48 weeks of the study and then every 24 weeks for the rest of the study. And it's a relatively sparse sampling schedule, not serial PK but just a few blood samples.

After completion of this double-blind placebo controlled period, all patients may transition over to open-label active treatment with weekly IV infusions of active drug for an additional 96 weeks. As I mentioned, the primary endpoint for this study is change from baseline in 6-minute walk test distance.

Another important design feature to emphasize, is that we really wanted to minimize the duration of the placebo period as much as possible. We built in an interim efficacy analysis to take place when 75 percent of patients have reached week 48; and then they'll be reviewed by a firewalled independent data monitoring committee. But if there's really overwhelming evidence of efficacy, then the double-blind placebo controlled period of the trial can be stopped there; and all patients, then, could roll over early to open-label active treatment.

Many of these points have been spoken to in previous presentations. But just to give an overview again of what we're really striving for in terms of venous access for Duchenne patients in the ESSENCE trial. Because this is a really long duration study, and because the schedule of infusions is weekly, it's really important to have reliable venous access so the patients can continue to get their infusions. And also, to be able to provide blood samples for the ongoing safety laboratory assessments that are

required for the duration of the study.

But, of course, another really critical goal to keep in mind, given this frequency of infusions and given this frequency of lab draws, is to really minimize the pain and suffering of the patients participating in the trial. And this was very, very compellingly spoken to by many of the presenters earlier today.

But there's also an important medical consideration to emphasize and that is, that because of the many comorbidities that Duchenne patients have, they're going to require IV access in the future. Preserving the integrity of peripheral IV access as much as possible now, by avoiding multiple attempts at peripheral access and the potential scarring that can result, this is really critical for the future medical and surgical needs of these patients.

It's hard to speak after everyone else because much of it has already been said. But really there's many, many factors in Duchenne that add to the challenges, and that can compromise being able to secure and maintain venous access. Just on the basis of the disease, the mobility limitations, the contractures that can occur. The steroid-induced vein fragility that's been spoken to today, with chronic corticosteroid treatment, also Cushingoid features with obesity and fat accumulation.

And then going along with the disease also, some cognitive behavioral and psychiatric issues, be they learning disabilities, be they ADHD, prone to anxiety and panic disorder, autism spectrum disorders. And the steroid treatment itself can also induce mood lability, tendency towards aggression, et cetera. This is a very challenging situation.

Because ports have been placed and used in all of our prior Sarepta

Duchenne's studies, we've systemically collected information on port usage across all the studies we've done. The data include details on port placement, port replace and removal, as well as the reasons for port placement.

The options for reasons for port placement include initial access, so the port was placed proactively at the beginning of the study; could be placed because of loss of IV access, or patient/family preference, physician preference or other. Now we use this data to understand the prevalence and pattern of port use across our Duchenne trials in order to estimate the likelihood of how often ports may be needed in the ESSENCE study.

In our analysis, we focused on the group of patients most relevant to ESSENCE. Let me walk you through this analysis step by step.

Starting at the very top, the blue box, we first looked at patients who had at least 48 weeks of treatment and this totaled 124 patients. And then of those, if you move down to the right those who started with the port -- sorry started without a port -- was 70 patients. This is also analogous to those current ESSENCE patients who've been in the trial without a port so far.

And then we wanted to look at the port usage over 96 weeks, which corresponds to the 96-week double-blind placebo controlled period of ESSENCE; so, patients who had ports placed by week 96. That was 30 patients. So we also want to understand why ports were placed in these individual patients. The data showed that of the 30 patient ports placed in the first 96 weeks, 22 were due to patient family preference and 7 were due to frank loss of peripheral access.

Although the loss of access in 7 out of a total of 70 patients may not seem

like an overwhelming high number, this occurred despite attempts to minimize loss of peripheral access, and in a setting in which ports were allowed. In a context in which ports are not allowed, the rate of frank loss of access is likely to be higher.

The most common reason for port placement was patient and family preference. Our understanding from investigators and study coordinators, and very, very much in line with all of the experiences that have been talked to earlier today, it's really situations in which IV access is becoming increasingly challenging. And ports were elected to be placed rather than either undergo many, many more very painful attempts at securing of peripheral access. Or in cases when it's really at the brink of losing access altogether, that a port needs to be chosen.

Another really important factor to consider, in the pattern of port usage, is the timing. We wanted to understand the timing of port placement within the first 96 weeks to get a sense of the potential impact on ESSENCE.

As shown in this slide, of the patients treated for 48 weeks at least and who had a port placed reactively during the study, the vast majority, about 83 percent, had their port placed within the first 48 weeks. In the median time to port placement, half of the patients had their port placed by 15 weeks. This is very, very early in their trial experience; and so, this really underscores the fact that IV access is lost early and particularly emphasizes the urgency to address this issue in ESSENCE.

In addition to collecting this data about port usage, and timing et cetera, we also compiled data on port safety. We approached this by identifying adverse events that might potentially be associated with port placement or use. And this slide summarizes the experience across our Eteplirsen intravenous studies.

The right most column shows all patients treated with an Eteplirsen IV. And the central column shows, of those patients treated IV, those with ports. Overall, there were 148 study patients treated with IV Eteplirsen, 86 used a port; and of those 86 patients with ports, 32 had port-associated adverse events. None of those adverse events were serious.

But if you really look at the middle column, the port column, and then the all IV patient column on the right, really the AE profiles are quite similar. And the nature of the adverse events is really what you would expect to see in the context of the IV access generally. There was one exception in which there was a discrepancy between the rates of these kinds of events. In the all IV group, everyone who had IV, either peripherally or port, versus the port group, and that was procedural pain and rash. These data suggest that peripheral IV access was actually associated with a higher rate of procedural pain and rash than was port use.

While we don't have a great deal of data from our other exon skipping development programs, we do have information from a small 12 patient study of our exon 45 skipping drug SRP-4045. This is being conducted in the US, and it is enrolled advanced stage DMD patients.

In this study, 11 of 12 patients used a port and 5 of the 11 port patients had port-associated adverse events. Of note, one patient had three serious adverse events of bacteremia, septic embolus, and vena cava thrombosis.

We looked carefully into this case further and learned that the patients port had been placed by a surgeon who didn't have extensive experience with port placement in DMD patients; and the port hadn't been anchored properly. Fixing the port in place

can be challenging in advanced patients because of lack of muscle to firmly attach it to. But this is something that surgeons experience placing ports in DMD patients can deal with.

This case really highlighted to us the need to have only surgeons with DMD expertise place ports in our studies; and we've reinforced this point during orientation and training with our study investigators. We're trying to apply the lessons learned from our port experience to ESSENCE and other studies moving forward.

Considering all the information we've heard today, be it our Sarepta US trial experience, the broader port experience understood from practice settings from the medical literature, there are indeed risks associated with port placement and usage. But it's also important to recognize that precluding the use of ports in ESSENCE has its own consequences as well.

Much of this has been covered, again, very eloquently earlier today. But I'd like to focus on a few topics related to the trial itself.

When ultimately peripheral access becomes non-viable -- which based on our previous trial experience we expect could occur within the first two years in a substantial proportion of patients. The result and withdraw of those patients could really reduce the value of their contribution to the trial. They're leaving early and what they've already given to the trial is essentially lost. But beyond that impact, individual participants dropout due to loss of peripheral access could also affect the conduct of the larger trial itself.

If you have a high dropout rate, this requires a large sample size and this is derived from an already small pool of eligible patients; and this in turn can challenge the

feasibility of the trial. And ultimately, if there are too many missing values because of dropouts, the whole validity of the trial, the entire trial could be compromised.

To address this, we've proposed some language that would allow optional use of ports, only as necessary and at the discretion of the investigator and also, of course, the patient and family input is absolutely critical in this process. Here is some potential protocol language we've put in a proposed amended protocol, but this is something that is up for discussion and deliberation among the committee today. And we really look forward to suggestions, refinements, to the approach and to the language.

To sum up, we know that maintaining IV access is challenging in Duchenne patients particularly when frequent infusions, frequent laboratory draws are required, et cetera. Allowing investigator discretion regarding port placement can minimize the physical and emotional suffering that patients experience. It can reduce the risk of permanent loss of venous access, and this is really important given that patients will have ongoing medical and surgical needs throughout the course of their disease. From a trial standpoint, it would prevent dropouts due to loss of venous access and this would really help preserve the validity of the trial.

Our proposal is very consistent with what you've already heard today, that ports be permitted in ESSENCE as necessary; really on a case by case basis according to the judgment of the investigator and in discussion and consultation with the family.

Thank you very much for your attention.

**DR. HUDAK:** Thank you. Questions? Dr. Hoehn.

**DR. HOEHN:** I have one clarification -- Sarah Hoehn. I have one clarification and one question. We've been hearing today about previous trials that allow

the use of port and that you've had multiple ones, both the one at Dartmouth that the family talked about, and another one where they've used ports.

And just so I'm sure I understand everything, at those times -- because it made me think of what the person from UCLA IRB said this morning, which was that, in the prior studies that used port there was no evidence of benefit. So, the difference between those studies that allowed a port, and this study that precludes a port, is that this is placebo-control. I just want to be sure that I understand the difference.

**DR. LAFORET:** That's right. All of these other situations and trials, in which ports have been used, have been in the case of open-label, active treatment.

**DR. HOEHN:** Okay. And then my second one is, I didn't know if there was any experience doing IM injections. I didn't know how long the infusion run, if it was four hours or four minutes in terms how long it lasted? And whether or not you had any evidence, in terms of whether or not it could be given intramuscularly or other avenues besides venous access?

**DR. LAFORET:** Very first inpatient trial was IM, just a single injection; but the administration paradigm has been IV ever since, and the duration of the infusion itself is 35 to 60 minutes.

**DR. HUDAK:** Dr. Fost.

**DR. FOST:** Assuming that the port requires 407 panel, and there are some who might disagree with that; why was this not anticipated a year ago? That is, why did you not try to convene this panel a year earlier rather than wait for this to unravel the way it is.

**DR. LAFORET:** At the time there was initial deferral by a central IRB.

We had a discussion with FDA in October 2015, with the central IRB, Sarepta, and Division in Neurology Products, and ethics colleagues as well at FDA. The option then was to -- essentially, is there another central IRB that would approve the trial which is how that turned out, but FDA has made this very categorical prohibition.

I think there were concerns about delay to the start of the trial, et cetera. And I think we've gathered a lot more information now about the pattern and timing of port use that puts this in much starker perspective, especially the lived experience in the ESSENCE trial so far.

**DR. HUDAK:** Dr. Joffe.

**DR. JOFFE:** So a question I asked Dr. McGough earlier is, the vision that if this is approved, that Sarepta will pay the cost associated with port placement and removal and all of that?

**DR. LAFORET:** That is correct, that is right.

**DR. JOFFE:** Thank you.

**DR. HUDAK:** Dr. Turer.

**DR. TURER:** In the absence of receiving these infusions -- and perhaps I don't know if you would be equipped to answer this. What is the frequency with which patients with Duchenne need blood draws and or infused medications?

**DR. LAFORET:** Outside of the clinical trial context?

**DR. TURER:** Precisely.

**DR. LAFORET:** That something I would have Dr. Shieh speak to in that he's directly involved in clinical care.

**DR. SHIEH:** Perry Shieh, for identification purposes. Routine laboratory

work we've been doing typically for standard care assessments in patients, in our clinic, once every six months.

**DR. HUDAK:** Dr. Turer.

**DR. TURER:** Christy Turer. Quick follow up question. Are those just peripheral sticks, not IV placements?

**DR. SHIEH:** Yeah. Generally, patients who are just receiving routine care, and do not require regular infusions, do not have a port placed. So there's no-- what we've been doing is just regular phlebotomy.

**DR. HUDAK:** Dr. Foley.

**DR. FOLEY:** Aileen Foley. Just wondering if you can give us an idea of when you anticipate the interim analysis, when they have 75 percent of the patients on study drug for 48 weeks?

**DR. LAFORET:** We have a very coarse estimate. It really depends on the remaining recruitment time for this study. It's hard to give anything very meaningful. As you've heard, we're about 1/3 enrolled. We have many more sites coming up over the coming months, and of course that timing will determine when patients will come in. It's hard to give a specific time, but it also reinforces the importance we're trying to place on enrolling quickly to get everybody to that milestone quickly. But as far a concrete time, it's a bit hard to nail down at this point.

**DR. HUDAK:** Ms. Celento.

**MS. CELENTO:** Amy Celento. You made reference to the expertise needed to place a port in a DMD patient. And I'm just curious, do you have any understanding of how many of those experts exist, and where they're located? And how

would patients get access to that level of expertise?

**DR. LAFORET:** From the Sarepta prospective, it would be just within the confines of our clinical trial experience and the surgeons that we have worked with who have worked through the studies with us. Who have developed their own best practices, or better practices, I guess, I would say overtime; so, we have those identified.

That does not mean that other sites couldn't either also do ports or have the requisite expertise. It would be the investigator who best knows his colleagues, et cetera. And we would guide as far as the best practices that we've learned so far. But the investigator would be positioned to identify appropriate surgeons who have the requisite level of sophistication about DMD issues.

We do provide support of information, some guidance about anesthesia risk, et cetera, sort of the medical decision about who is an appropriate surgeon in consultation and guidance and support from us. But it really is the investigator's responsibility for the safety of his patients or her patients.

**DR. HUDAK:** Dr. Levine.

**DR. LEVINE:** Rod Levine. In the proposed language you have for the protocol, it begins with the phrase "In the event it becomes necessary." Given the information you've just shown us, and all of what we heard this morning, would you consider dropping that phrase and simply letting the investigator and family determine if and when a port would be placed?

**DR. LAFORET:** Truly that would be in our estimation the ideal scenario as well. This was very conservative language, intentionally. And it's intended as a starting point, really, for the discussion. I think from the Sarepta standpoint, allowing

broader latitude and even proactive placement, if it were judge appropriate by the investigator, would be acceptable and really ideal for us.

**DR. HUDAK:** Dr. Cunningham.

**DR. CUNNINGHAM:** Melody Cunningham. On that same paragraph, we've talked most in the family's experience as well as what's been discussed here about port placement. And then the paragraph talks about mid-line catheter, which doesn't have a very longevity. It seems uncomfortable to have that as an option. Central line, perhaps, we can discuss. But I'm just wondering why we've talked all about port-a-cath, and then we have suddenly these three options in the paragraph.

**DR. LAFORET:** Again this was intended to be very conservative, and inclusive, as a starting point, but to be refined based on the input and evidence that we have before us -- again, starting place only to be inclusive.

**DR. HUDAK:** Question. Thirty patients are enrolled in this trial currently; could you give us a breakdown -- obviously, there are five, I think, that are UCLA. How many of the remainder are patients in this Country? How many are international patients?

**DR. LAFORET:** These are all US.

**DR. HUDAK:** These are all US?

**DR. LAFORET:** Right.

**DR. HUDAK:** And then of the other 25 patients, non-UCLA, are there any of these patients that have been treated with the help of central line or port-a-cath?

**DR. LAFORET:** In ESSENCE, not, not at all.

**DR. HUDAK:** No? Okay.

**DR. LAFORET:** It's still under this FDA preclusion stipulation.

**DR. HUDAK:** Okay, thank you.

**DR. LAFORET:** Thank you.

**DR. HUDAK:** We'll move on to Dr. Nelson who is going to give the committee its charge.

## **PRESENTATION OF QUESTIONS TO THE COMMITTEE**

**DR. NELSON:** So while Cathy is calling up the original slides that have the two questions -- our understanding is that the intermittent "brown-out" -- let's call it -- of the slides is being actively monitored; and that's why you see them suddenly reappear in a magical way. There are people outside the room that are watching this and they press some magic button to restore it. We're not sure what that interaction is due to, but try to ignore the fact that it's coming and going. Sort of reminds me of the Wizard of Oz; ignore that man behind the curtain.

What I'd like to do is present the two questions and perhaps explain to you why we did it this way, and maybe it will then fit into your understanding of the conversation.

The first question is a voting question. And I'll just read it. Use of an indwelling central venous access device -- which is left purposely vague -- in the ESSENCE clinical trial should be allowed? A yes vote here would mean that you, individuals who might be voting yes, could imagine circumstances under which an indwelling central intravenous access device should be allowed in the ESSENCE clinical trial. That would be the consequence of a yes vote. A no vote would be that, under no

circumstance do you think it should be allowed; so, that would be a no vote.

Now, the reason we did this, I think, can be clear from looking at question two; which is changed on this computer, but not changed on yours, so -- is there a time lag? Yes. That man behind the curtain is now pulling the buttons and you will see question two shortly.

**DR. HUDAK:** And this may be the last slide we have to deal with this, right.

**DR. NELSON:** Yeah. But they're supposed to remain displayed during your discussion so we're not over this sort of off and on thing, although you have it written. You know, bells are being pulled, the tinman is shaking -- no, he was the one without the heart; the lion was shaking, sorry. Anyway, it will come up soon.

Question two; so our purpose in dividing this and making this non-voting, and then I'll read it, was, you know, each one of us may have a different threshold. So, is three times failing in two visits, and five times in one visit right, or should it be two times in two, or some have said should it just be proactive? Or others might say could it be four in two, or maybe it needs to be six in one. You could imagine the complexity a) of trying to create a vote around all of those potential permutations, not knowing what you all think and, you know, to try and set a series of voting questions on each of those aspects, I thought would be daunting.

And then the other question is, if in the protocol itself there are some stipulations, then it also places the local IRB in having to say do we approve or disapprove and it gets into protocol modification. So I think there's some procedural issues that would relate to the extent to which in the protocol that should be stipulated or

not, setting aside the issue of device. I mean, that could easily be something that you might want to discuss.

But, you know, should the protocols say three instead of four or twice and once? I mean, if it did the IRB -- and just procedurally, just remind you -- the IRB that disagreed with those stipulations would have to disapprove the protocol, and then would have to ask for modification which would then have to go through all the other IRBs. So, there are some procedural issues to keep in mind.

I was talking too long and it disappeared on me, but I will read it again because I assume the button to be pressed is easier now. So question two we then framed as a discussion question. Now, if there's some points of consensus that emerge, I think they can be identified, but we didn't think it made sense to structure that as a vote process because that would take a fair amount of procedural time, and so that's why we did that.

And so we outlined some considerations for you to address and we tried to place them in a certain order of sequence that made sense, although you could decide to take them in a different order. So these are the following issues:

Should the choice and timing of placement of a clinically appropriate central venous access device be left to the discretion of the study site investigator? And I appreciate this would also be obviously in consultation with both the parent and patient around that, but should it be at discretion.

Should the protocol include criteria for deciding when an individual study participant has difficulties with peripheral intravenous access or DIVA, which is often abbreviated that way, such that the use of a central venous access device may be

appropriate?

If the protocol should include such criteria, what type of criteria ought to be specified, number of failed attempts, number of visits, use of alternative visualization technologies? Much of what you've heard UCLA have gone through already to come up with their approach.

And then, how should the burden, of undergoing multiple failed attempts at establishing peripheral intravenous access, be taken into account in terms of anticipatory anxiety, post-traumatic stress?

Now, we didn't put the specific device in here, but that could also be something that would be appropriate to discuss. Is there a second slide to this Donna or is this the complete question?

Okay. That was the idea. In other words, a thumbs up or a thumbs down about putting into the protocol the possibility of a central venous access device; and then a broader discussion if the committee thinks that the answer or -- you know, if everyone votes no, we're done.

If enough people vote yes to where it's worth getting that kind of feedback, then I think having a broad discussion of that would help inform us in working on what that Commissioner determination ought to be, and then to work with the sponsor around that protocol should be framed. I'm happy to take questions about why we did it that way, but that's why we did that way.

**DR. HUDAK:** Dr. Hoehn first.

**DR. HOEHN:** I have a clarifying question. Indwelling, does that include temporary lines like IVs and subclavian, which we haven't talked about at all today? Or

does it only talk about a line that can leave the hospital? I just want clarification around the word “indwelling”.

**DR. NELSON:** Our intent was around the kinds of ones that Donna listed in terms of PICC lines. Yeah, the idea would be ones that could leave the hospital. It would be indwelling. I mean, strictly speaking, a peripheral IV is indwelling during the time it's in place. You're right that there's point of ambiguity there, but yeah it would be in for longer than the infusion time.

**DR. JOFFE:** Steve Joffe for identification. I have a procedural question for what comes after this meeting, and this vote and the FDA's decision. If the vote is yes, there are circumstances and then we have a discussion of what sorts of criteria, the things that are on the slide. Is the, sort of, procedure here that there will be one standard that every institution has to then either accept or reject the protocol? Or is there going to be room for individual institutions to have discretion about different criteria for when a port or other device would or would not be placed?

Is the ultimate outcome of all this going to be a single standard that institutions either have to accept or not? Or is there going to be room for individual institutional discretion?

**DR. NELSON:** Well, let me answer that two ways but the first one is simple. I mean, to some extent, if all of you agree that there should be a single standard, I mean, that's something you can certainly say; or if you thought there should be an institutional, sort of, more permissive stance that it should be allowed. But, you know, within constraints, or just simply at discretion, that's something that would be important for this discussion.

Procedurally, what happens is they'll be -- you know, an FDA Commissioner makes a determination. The process for that is, when we consider everything, this discussion, our reflections, the public comments, our office will draft a letter that would be proposed to the Commissioner as the determination. And then that letter would be addressed to UCLA, with a copy to Sarepta, and would be posted publicly. That's the process.

What's in it? I mean, and I should also say that every IRB would still have the authority to then approve or disapprove of that protocol, which would be their purview, regardless of what was put in there. It's simply, the FDA action would certainly allow it to go forward if that was the decision, but it would still require IRB approval to go forward as well. Does that answer your question?

I mean, if you think it ought to be restricted and have very strict criteria, that's something you can certainly say. If you don't, I mean, that's something to be as part of the discussion.

**DR. JOFFE:** It mostly answers my question, but let me just ask one, sort of, follow-up which is, if the vote is yes, and the Commission's decision is yes, and then that letter goes to UCLA with copy to Sarepta, could the final protocol that comes from Sarepta, as amended, allow institutions to have discretions around the criteria? Or is that impermissible by whatever rules apply?

**DR. NELSON:** I think that's certainly a possibility, it's on the table. I'll confess, I mean, when they asked about submitting the amended protocol I suggested they not include specific details because I thought there would be significant variability on that.

**DR. HUDAK:** Dr. Turer.

**DR. TURER:** Christy Turer. One of the questions that I have, in part because I've been on the receiving end in internal medicine of having a patient who comes to me with a port-a-cath that is no longer needed. If we make this determination, if we said yes, what would happen at the end of the trial? What if a family says we don't want to remove it? For example, you know, I think, we need to also consider that and make sure to address that piece of it.

**DR. NELSON:** I think it's an issue. I'm not sure that it's something that has to be sorted out here. But I would imagine there would then be a discussion with the clinician around whether that port is useful or not, and to what extent it then present risk only. But certainly if -- I mean, we're talking four years from now. It's hard to know what's going to happen four years from now with the product and the like.

I know there are parents who were on Eteplirsen who are waiting to know whether it would or wouldn't be approved, to decide whether or not to put a port in; because I got a phone call on that exact issue. I didn't know the answer because it was two weeks before I learned the answer. That's a decision that parents are gonna have to make.

**DR. HUDAK:** Dr. Fost and then Dr. White.

**DR. FOST:** Norm Fost. Back to Steve Joffe's question. It seems to me that how that works out depends on how we answer these questions. If the big question number one is answered yes -- let's say there's either a unanimous approval for that yes, it's okay under some circumstances. And if there were unanimous approval for 2A that that should be left up to discretion, then that allows any IRB to down regulate that in any

way they want, but it makes anything possible. I think, how much flexibility there is to IRB depends how this committee responds to mainly those two questions.

**DR. WHITE:** Michael White. Just help me a moment Dr. Nelson; the process is, we make our recommendation or our determinations, it goes to you --

**DR. NELSON:** You make your recommendation --

**DR. WHITE:** Right. And it goes from here to you and the Commissioner. The Commissioner then publishes a comment period --

**DR. NELSON:** Since UCLA is the referring IRB, they will get a letter with a copy to Sarepta that includes that determination.

**DR. WHITE:** Is there a period of review, public review or not?

**DR. NELSON:** It will be posted publicly. There's no period of review without determination --

**DR. WHITE:** That's what I was trying say --

**DR. NELSON:** This is --This is it.

**DR. WHITE:** That's fine.

**DR. NELSON:** And I can actually -- well maybe Norm is going to suggest this, but you -- whether or not we accept your recommendation is something that we can determine one way or the other.

But it will be posted publicly and I have my own timeline of when I would like that happen. But knowing what's going on with User Fee legislation on the Hill and what the new Commissioner that we have, as of last week, has to do, I don't know when I will get on his schedule. I have my hopes, and I'll tell what that is. I hope by the end of next week, but that's just me.

**DR. HUDAK:** Dr. Sayej and then Dr. Cunningham.

**DR. SAYEJ:** I think everyone's response here is, if we all say yes to this, this is specific for the ESSENCE clinical trial. But this will also have implications on future trials for other medications, I'm guessing.

**DR. NELSON:** Well, let me speak to that; that's a very interesting question. There's two issues here. I mean, you saw the timeline Sarepta presented and there had been a conversation back in November 2015 about this.

I planned to ask -- and since PPMD put this on their blog it's public; I'm not saying something I didn't say to them and now everybody knows. I plan to ask OCC, which is our lawyers, as to whether or not FDA could initiate this process. Instead how we've traditionally interpret this as being an IRB referral, it's necessary to initiating it. If we could have initiated the process on our own, we could have had this discussion back in November 2015. All right? That's the first point.

Second point is, we've never had a case where we've been able to say a precedent. There's nothing in 5054 that says the panel has to meet before or after the protocol is submitted. Now obviously, Sarepta's development strategy -- I'm not sure what the next exon is, but I'm sure there's another on in line. It will be the same issue unless dystrophin has been proven as a surrogate to where you can do an open-label trial with a PK/PD or whatever, but let's imagine that you still need a blinded placebo, it's the exact same issue.

We've never had a circumstance, yet, that asked the attorneys can I apply this panel decision to a future protocol. It is my intent to do so.

All right, so they have not opined yet on that as being consistent with the

regulations. I think it is, but I'm not an attorney and I would need them to say that they agree. Does that answer your question?

**DR. SAYEJ:** Yes.

**DR. NELSON:** Now, whether it applies to other patient groups is an open question. Because I think you've heard very specific issues here around the problems of intravenous access that may or may not apply to another population. I wouldn't go so far as to say that this has any consequences beyond this protocol, absent extending it to other Duchenne protocols, once I ask OCC that question, which I plan to. But it wouldn't necessarily have any implications for other populations such as biological therapies for type I diabetes, and so on and so forth. Does that help?

**DR. SAYEJ:** That's exactly what I was asking for.

**DR. NELSON:** Right, yeah. But I think that's what makes this meeting important from my standpoint. Independent of this decision, it allows me to go to the attorneys and ask them two very important questions, that I've not been able to ask them, because they don't like to deal with hypotheticals. I now have a real question I can ask them.

## **COMMITTEE DISCUSSION**

**DR. HUDAK:** Dr. Cunningham.

**DR. CUNNINGHAM:** Melody Cunningham. Just a thought on the question of port removal. I mean, I foresee either this is effective and the port would remain in for ongoing therapy; or it's not effective and then the medical complications would become higher and the need for access to treat some of those medical

complications and perhaps other interventions would be needed.

**DR. HUDAK:** I think Dr. Moon may have joined us by phone.

**DR. MOON:** Yes, I'm here.

**DR. HUDAK:** How long have you been on the line?

**DR. MOON:** Oh, about 20 minutes.

**DR. HUDAK:** Twenty minutes. At this point, could I put you on the spot and perhaps ask you as our surgeon, for any other additional comments that may amplify what others have said about specifically central venous lines and port-a-caths as tools in this protocol.

**DR. MOON:** Yeah, you mean in regard to risk and access and other alternatives, right?

**DR. HUDAK:** Correct. And maybe, specifically, from your experience with port-a-caths, you know, what's your experiences with longevity and complications.

**DR. MOON:** The complications, I think, are small. The issue of infection is one that's rare, especially if it's not used excessively, and the patient is not immunocompromised. The second is the actual placement, probably the pneumothorax, which is a benign complication, no long-term consequence, which is also rare. I forgot how old these are kids going to be. Are they teenagers or 5-year-olds?

**DR. HUDAK:** Seven to 13.

**DR. MOON:** Seven to 13. They may very well be done with cut downs for the most part. They'll get a small incision, anesthetic risk, you know, zero essentially. And the long-term risk of thrombosis of the vein is, I think, really unheard of, pretty much, unless the patient has got a clotting disorder.

In that regard, the complications from a technical standpoint, from a surgeon who does these in children, and that would have to be a mandatory thing, that it's not a general adult surgeon, but it would have to be a pediatric surgeon who places these lines.

Essentially, it's something that the heart surgeons generally do at the end of the day. Because it kind of doesn't take very long and they can kind of fill in the gap to do. In an adult, you could essentially do it under local anesthetic, but obviously in a seven to 12 year-old, you wouldn't want to do that. I think anesthesia long term consequences are zero. I think, pretty much; unless there was one of those hypercoagulable states. Even if it got infected all you do is take it out, which is quite rare as well.

It's difficult, I think, as far as other aspects of doing it in a -- someone who doesn't have to have it, obviously is the issue. But I think the downside is negative -- the only way out of it is to not have it be a blinded study anymore and I don't think that doesn't seem to be a good viable option.

**DR. HUDAK:** Dr. Sayej --

**DR. MOON:** Is there anything more specific?

**DR. HUDAK:** Yeah, I think we have a question from Dr. Sayej.

**DR. SAYEJ:** Hi Dr. Moon, this is Wael Sayej. I just want to ask a question. Dr. Laforet, from the sponsor, presented something earlier about some of the complications that can occur with placement of port-a-caths or central venous catheters. And one of the points that she raised is, you need an expert or someone who has expertise in placing port-a-caths in patients with Duchenne, DMD. Knowing how rare

this disease is, my guess is that there are not many people who have that expertise or have done enough to call themselves experts in DMD specifically. In your opinion, how many of these in DMD patients -- well couple questions. Number one; how different is it to place a port-a-cath, for example, in a DMD patient versus a non-DMD patient? And number two; how many of those would have to be placed to claim that you have expertise in doing so?

**DR. MOON:** I think it's not a matter of actually being a DMD patient, it's just -- it can be a little unusual anatomy. I think that the standard patient with absolute normal anatomy can be done percutaneously without visualization. The issue with the abnormal anatomy is that it would have to be more surgically placed. I think that it would need to be done either by someone with little experience or -- almost nobody is going to have experience doing that typically. But surgically, if you do surgical cut down through the vessel, you're not going to have the issues with anatomy that you would have with a percutaneous approach.

I think it should be done in an operating room setting, under general anesthesia, by a surgeon with visualization. I don't think any particular number of port-a-caths, specifically in a Duchenne, is going to be obtainable. I think somebody who has experience placing port-a-caths, in general, would be able to take care of it. And I would say it shouldn't be the person whose put in five of ten. You know, I think if you've put in 30-40 port-a-caths, you're probably very well experienced at it at and could do it safely.

**DR. HUDAK:** Dr. Cunningham.

**DR. CUNNINGHAM:** Melody Cunningham. Dr. Moon, so one of the

things that was discussed earlier, when you weren't able to be here, was about the placement of the port-a-cath in patients with limited muscle tissue; and that that was one of the issues from an expertise standpoint. But I wonder if you could comment on how a surrogate of a very cachectic patient, or a patient with other neuromuscular degenerative disease, might be a surrogate for expertise in placing these port-a-caths.

**DR. MOON:** I think the issue with the severe muscular limitation is mainly one of not finding the vein, or putting it into the vein. It's a matter of the port-a-cath potentially pressing up on skin, maybe causing some pressure on it, because there's not a buffer of fat tissue and muscle. I don't think it actually affects, too much, the surgical placement. That probably just affects more the cosmetics and the possibility of fat erosion, pressure ulceration over the device, I think.

I don't think that that will effect too much the surgical placement. Actually, it probably is easier to put it in in somebody who's got muscular limitations than someone who is muscular -- because the vein is going to be, you know, down there regardless, and you won't have to get through so much tissue. I don't think it will affect placement too much out of the ordinary.

**DR. HUDAK:** Dr. Sayej.

**DR. SAYEJ:** This is Dr. Wael Sayej again, just one last question. Since the complications rates with -- or the risk of infections, or clotting, or mechanical failures for PICC lines, central venous catheters, and port-a-caths are different, in your expert opinion if you were to place a single device in -- or venous access in patients for the study, which one would you pick?

**DR. MOON:** Yeah, I would pick a port-a-cath. The reason being it's not

exteriorized, so it's far less exposed to infection risk or trauma. Often times, in patients -  
- at least adults or children who are going to get multiple blood draws -- we can place it  
and just leave it. It's not like when they're done with their treatment we necessarily go  
in and take them out. We leave them because it's benign to leave it.

The other ones you have to take back to surgery and take out for sure. The  
port-a-cath you can leave in if the child is going to get other blood draws and more  
treatments down the road. I think it's a more long-term solution and has less infection  
risk than the others.

**DR. HUDAK:** Any other questions for Dr. Moon? Okay, hearing none, I  
guess we can move on to the discussion.

I'd like to sort of maybe sketch out a few of the things that I have  
understood and that I've heard before we do the discussion, and let Dr. Nelson correct  
me where I stray at the wrong path on this, especially with regulatory issues. But what I  
think what we've heard today is that this is a referral made by the UCLA IRB about this  
protocol with respect to the use of alternative venous access devices that are not covered  
under the protocol. They could not see their way to approving this through CFR 21-  
50.51, 50.52 and 50.53. And just to go through that a little bit, I think that they were  
very careful in understanding that the FDA had guidance that this particular procedure of  
placing and maintaining such lines presented more than a minor increase in minimal  
risk. And therefore they were compelled, in going through the logic of the regulations,  
to refer it to this committee under the procedures outlined in sub-part D-50.54.

So, 50.54, just to refresh everybody's memory on what that says, is that if  
an IRB does not believe that a clinical investigator within the scope described in 51, 52,

53, this investigation may proceed only if the IRB first has to find that the clinical investigation presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children, which the IRB did and was very clear about that.

And b) the Commissioner of the FDA, after consultation with the panel of experts and following opportunity for public review and comment, determines either -- and here is where we get into the eithers -- number one, that the clinical investigation, in fact, does satisfy the conditions of 50.51, 50.52, or 50.53 is applicable, which in my understanding would mean that the committee would find that this would be a procedure that was a minor increase to minimal risk.

Or, taking that out of the picture, that the following conditions are met, and there are three of them.

One is that the clinical investigation presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health and welfare of children, which the UCLA IRB has opined on. Two, that the clinical investigation will be conducted in accordance with sound ethical principles. And three, that adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians is set forth.

I read this regulation to say that, even if the committee determines that this addition to the protocol presents more than a minor increase beyond minimal risk, that we could approve this. Two other things and then Skip can comment.

The two things that I've heard today are that -- correct me if I'm wrong, Dr. McGough -- is that your IRB had said that it could find its way potentially to finding this

to be a minor increase to minimal risk procedure. I think I heard that.

And number two, the thing that I think has impressed us all in this meeting is that the risk benefit ratio of continuing to do peripheral IV access for drug administration has a very, very -- compared to placing a port-a-cath for instance -- has a very, very different coloration in the real world than what we might sort of take away from the paper version of the protocol.

That risk benefit changes, I think, dramatically in the context of this particular study with this particular patient group. Those are some of my takeaways from this morning and this afternoon. Skip, please correct me.

**DR. NELSON:** No, the takeaways are fine. I just wanted to make a clarification. We are not asking the committee to opine as to whether this fits under 51, 52, or 53. If someone thinks it might, feel free to vote yes, but we're not asking you to make that determination. I would assume if you want to have a discussion about reasonable opportunity, you're right, that is one of the findings; but I would assume if you voted yes that you think that's the case.

And as far as sound ethical decisions, my experience in asking that question in other reviews under 407 and 50.54 is that it's interesting to hear some of those ethical questions, and that would be important to know why people voted the way they did. But it often is simply repeating things like the importance of parental permission and child assent and the like.

Two other comments; on the parental permission and child assent form, I mean, we did not ask for a revised consent form including this, simply because we felt that would be potentially busy work if this committee thought that it was not appropriate

to move forward. And that would clearly be dealt with if it is allowed to go forward.

And if are there any comments; I mean, we heard some about what ought to be in those forms. I'm fairly confident that we could work with the sponsor on a template that the IRB's could use around appropriate informed consent. If people feel strongly that there's certain components there that ought to be in there, I think that would be important to be part of the discussion.

And then -- what was the -- I lost track of -- well maybe the other thought I had might come back to me. Oh, yeah, the other thing is it's very important to keep conceptual clarity around some of these distinctions. The assumption is that something that moves forward under 50.54 is in fact ethical. You know, so it's inappropriate to say that somehow if it doesn't fit in one, two, or three that it's unethical. It's simply unapprovable by the local IRB; so that's a very important distinction.

And to say that the risk/benefit of the procedure may be favorable, and perhaps -- at least as or more favorable then, as some people pointed out, multiple attempts at peripheral IV, is not necessarily to say that is a minor increase over minimal risk.

I think, at least from my perspective, seeing all the protocols get through FDA, you have to ask what's the general implications of applying those principles. And with all due respect to the IRB community, I think often if they think something is ethical, they try and fit it into the three that they can approve, rather than use this process. And, you know, my bias is we ought to use the process when appropriate. But I don't think it's on the table to ask whether or not it fits under 50.53; it's not on the table. That's why you don't see a question on that point.

**DR. HUDAK:** Okay, so we can commence the discussion. Dr. Fost, I see you, yes.

**DR. FOST:** Thanks, Norm Fost. I want to make two comments, one about the ethical issues and second the regulatory issues. And the first comment is, I think it's very important to separate those two, they're not the same. I mean, we all have hundreds of examples of laws and regulations that are clearly unethical and that's why they change. Just because the Supreme Court said slavery is okay, we don't say, well that's the law I guess we've got to obey it. That is, ethics always trumps the law. We always should be asking whether the law is the regs, so even if the regs were clear, that doesn't mean they're right. I think our first task is to decide whether this is ethically defensible.

What if there were no regs at all? That seems to me a fairly simple question. You have a child, a child himself who is able to articulate this, who has this horrible disease, enormous suffering, a slow terrible decline into death. There's a trial, even if it were just a placebo-controlled trial, forget the extension part, even if it was just a 50/50. You got a 50 percent chance of getting a drug that has a reasonable chance of helping you.

It seems to me a lot of competent adults would chose to do that; and a lot of very reasonable parents would choose to do that, even if they only had a 50 percent chance. And they'd go through a lot of burden to do that.

People agree to take chemotherapy that has only a 50 percent chance of ever helping you, even though that's considerable more toxic and dangerous than this study.

A 50 percent chance of getting something that's helpful is something that a

lot of competent people decide to do, and reasonable parents decide to do. In this case, it's way more than 50 percent, it's at 2/3's, 1/3's randomization. And then you got that least the possibility of the extended study that everybody will get.

It seems to me ethically it's a fairly simple choice, and we heard from a dozen parents. I don't know if they're representative or not of the DMD community, but they all didn't see this as very much of a dilemma; whether having a port-a-cath would be a show-stopper, and whether to take this 50 percent chance.

From an ethical standpoint, it seems to me pretty straightforward. Reasonable people might disagree, but I think it would be impossible to say that a parent was acting unreasonably if they put their child through this risk of a port-a-cath, minimal though it is.

Even if we go to the regulatory thing, it seems to me this is easily approvable. First of all, the regs as we know are not always right. They're problematic in many ways. Even if there were a reg that prohibited it, that wouldn't mean that it's wrong to do it.

Second, it's not at all clear that the component -- even if you use component analysis, and I was glad to hear Skip confirm, we're not here to discuss 50.53. That's not on our agenda, we weren't asked to discuss it. All that microanalysis that 50.53 calls for, is it minimal risk, whatever that means; is it a minor increment, whatever that means, we're not here to discuss that.

We're here to discuss 50.54. And if we're going to be strictly regulatory -- forget ethics -- we're just going to obey the rules. All 50.54 asks us to do is look at the ethics of it. It says, you know, is it a serious problem, yes, will assent of the child and

permission of the parents be obtained, yes. The only hard question left is, is it ethical? It doesn't ask for any of this component analysis and so on.

Even if there were component analysis, I think we could -- I mean, I could give lots of arguments on why I think component analysis is problematic, but I don't think we need to get into -- in fact, I think it would be inappropriate to get into it. That's why I was puzzled as to why the FDA, in their superb summary -- and I really appreciate the detail of it -- but why so much time was spent on component analysis. That would be very helpful if we were here to discuss a 50.53 problem, but we're not.

All 50.54 ask for is really an ethical analysis, and the ethical analysis seems to me pretty straightforward. Thank you.

**DR. HUDAK:** Dr. Joffe.

**DR. JOFFE:** So I actually find myself listening to the presentations this morning, and especially the presentations from patients, participants in the trial, family members who are representing them are quite upset that we are here and in this circumstance at this point. I understand the precedents here, and the procedural difficulties getting us to this point, but it seems to me like I wish this had been addressed as I think somebody -- maybe more than one person said -- at the beginning as oppose to now, when people have been put through what they have been put through.

I'm thinking back to a meeting we had a couple of years ago about procedural sedation. And one of the things that was buried in the -- so the question there was if procedural sedation is being performed to permit a research procedure with no prospect of direct benefit, how do we think about the ethics and risk level of procedural sedation.

And one of the things that was buried in the comments, and I was reminded in looking at the documentation last night, is that a statement from the committee that if procedural sedation is deemed not to be permissible in order to be able to accomplish, let's say an MRI or radiological procedure, but yet would be part of the clinical standard of care for obtaining that procedure, it should not be withheld in order simply to be able to make the procedure permissible.

And so the application to this case -- so I'm an oncologist and most of my patients have had some sort indwelling line whether a port-a-cath or something that comes out externally, a line that's brought out externally. When I think about a kid who is about to embark on a course of therapy that involves 96 weeks of weekly infusions, to me -- even if they don't have the complexities and the challenges of placing access that a kid with DMD has -- to me the standard of care for 96 weeks of weekly infusion is to offer some sort indwelling vascular device, whether it be a port-a-cath or a line that comes out.

And then to have, between the family and the patient and the clinician, a discussion. And some families, in consultation with their docs, might decide to go the route of the indwelling catheter, some might not. But the clinical standard of care is that with 96 weeks of weekly infusions, a catheter, an indwelling vascular access device is standard of care.

And here, the reason I say that I'm upset that we're in this situation is because that clinical standard of care that accompanies 96 weekly infusion, at least, that offer has been withheld; and it's my own view that it should not be withheld.

And, you know, we can talk about the regulatory mechanism, and in this

case, there will be a vote on 50.54 about whether it's appropriate. But my own view is, speaking to the ethics and setting aside the regulations, it ought to be part of the standard of care any time you're getting a 96-week infusion, whether that's a research infusion or a clinical infusion.

Even without all of the challenges of DMD that we've been hearing about today, that offer ought to be on the table and be part of a decision and a discussion between patients, research participants, their families and their clinicians.

**DR. HUDAK:** Dr. Diekema.

**DR. DIEKEMA:** I'll be brief. I would second everything Norm and Steve just said. And just wanted to add, as I went through these document, even before what we heard today -- you know, from my experience as an ER doctor at a tertiary care children's' hospital, where we're accessing central ports all the time and we're placing lines all the time, there was no question in my mind that on this kind of a protocol the lower risk option is a port-a-cath, not hundreds of sticks over the course of two years.

And, you know, I think one of the problems is when we talk about risk we sometimes tend to underestimate pain and suffering as we compare it to the possibility of a clot, or the possibility of infection being introduced, which are all low with port-a-caths. But, I think, if you give pain and suffering their due, there's no question in my mind, as Steve so nicely put it, that the port-a-cath should be the standard of care here. And I don't see anything unethical about offering that in this particular trial, which I think should be available to these families.

**DR. HUDAK:** Dr. White.

**DR. WHITE:** Thank you. I don't have a whole lot to add. I think, I'd like

to go back to the older things and get away from the regulations to the recommendations from the president's commission. And it says under the circumstances that we're in, the research presents an opportunity to understand, prevent, and alleviate a problem, and in this case an orphan problem.

We have a very small population of patients, or subjects. I think we all would agree on that, there's no question that this is important. And then after that they say the conduct of the research would not violate the principles of persons, beneficence or justice. I can't think of anything that is more evasive to one's autonomy, and just all of those issues, that holding a kid down over, and over, and over, and over again to start IVs against their will, even if they said yes, I want to do this. I think that became abundantly clear today.

The risks are there. Then you just have to go to the third thing which is, adequate provisions are made for the assent of the children and the permission of their parents or guardian. The families that have come forward today are clearly well-informed of the risks of a port-a-cath. I think as long as we provide adequate provisions for assent and provision of the family, I think we should go ahead and approve it, or recommend that it be approved.

**DR. HUDAK:** Dr. Fost.

**DR. FOST:** Two things; I want to just add one thing that I left out in my previous remark. I don't want anybody to think that if the committee approves wider use of port-a-caths for this study, that we're approving port-a-caths for any non-therapeutic studies involving children. If this was a study of a new dandruff remedy that required 96 weeks of monitoring, you know, I'm against it; but I would be against the venipunctures

too.

This doesn't necessarily displace the FDA's general caution about port-a-caths, I just think it should not be an absolute. Being cautionary about it is not to say that it should be prohibited, even for non-therapeutic studies. Again, I don't like the idea of framing this as a non-therapeutic study, even for the placebo group, because I believe in the whole package thing.

The other thing is just a caveat to the UCLA IRB. I don't think there's any chance of this, but they should be very careful about trying to approve this under 50.53. Because if they did that, as Doug said earlier, the venipunctures are way beyond any ordinary notion of minimal risk. If minimal risk could mean things that happen on a routine visit to a doctor for a health supervision visit, tell me when a doctor pokes you 150 times over a two year period with real difficult vein access. So this would be a placebo -- if you're going to take component analysis and 50.53 seriously, I think you'd be in a lot of trouble even with the venipunctures; but fortunately, I don't think we need to go there.

**DR. HUDAK:** Dr. Foley and then Dr. Turer.

**DR. FOLEY:** It's Aileen Foley here. Just wanted to say as a pediatric neuromuscular specialist, this is a very important trial. And I think that we have the duty to protect our pediatric patients through the research that's scientifically sound and also ethically sound. And, you know, they need to be -- very importantly, you know, case by case, I think, discussions and very careful informed consent, at its core it's really an ethical issue. And there should not be a need to endure pain and suffering just to have a chance to access a potential therapeutic.

**DR. HUDAK:** Dr. Turer.

**DR. TURER:** Christy Turer. One thing that I thought would be important, I think that's there's no question that there's a lot of pain and suffering involved with the IV placement. I also think that there's significant risk with the port placement that need to be made very clear during the informed consent process. Regarding that in the outside of this trial there would not be the need for, you know, weekly infusions and so forth. And the detailing of the risks involved and the experience through the prior trials in Duchenne's patients, and also in other literature.

I mean, I just quickly ran the numbers in cancer population at St. Jude's and, you know, 11 percent catheter related infections, 4 percent removal, some having to be replaced. And although in everything that I've read, I have not seen a death, I think it's important to consider that that is a possibility if a child gets sepsis, particularly if they are on steroids, and making that very clear.

Now, as a parent of a young child who does not want to take any medicines or get sticks, you know, I had to think in my own brain about what would I do. I wouldn't want my child to have all those sticks, so I absolutely think that it is a compassionate thing to do. I also think we need to really bare the risks and understand that there is potentially the risk that a child could have an untimely death, if we, you know, say that they can get a port for this.

**DR. HUDAK:** Dr. Hoehn.

**DR. HOEHN:** Sarah Hoehn. I have three comments. And I have to say when I prepared for this meeting, reading everything in advance, my initial thought was that you would never consider a port placement for a placebo. But I think that as we've

talked about everything we talked about today, I think the issues in terms of the number of sticks, the context -- and I think this goes back to what Dr. Fost was saying, if the consensus is that yes, absolutely this is okay, it's okay for the purposes of this trial in this context of progressive neuromuscular disease. It's not okay for, you know, ADHD, or whatever you're other problem is; like, you have to keep the population that you're dealing with the primary thing in context.

And then the other comment I wanted to make was, somebody's slide said that if they chose it, that it should be left to the investigator and parent what kind of line they have. But I think that you obviously need to include the patient and the parent, but you also need to include the surgeon or whoever is actually going to be doing the line. If a surgeon says no, I wouldn't do a port I would do this instead, or you know, there's reasons why they wouldn't do it, I think that needs to be weighed as much as everything else.

I certainly support doing it after everything we've heard today, but I think it has to be an awareness with the surgeon who has the right expertise that takes the anatomy and everything all into account. I don't like the idea of the investigator saying, hey I want this kid in the study you have to do a port because that's what they say you have to do. You know, if there's reasons anatomically that that might not be a good choice for that child, there has to be a way that the surgeon can opt out of that and say no, another line would be more appropriate.

So that's my only hesitation with saying 100 percent it must be a port. If there's other reasons, if there's anatomical or medical considerations, I don't like the idea of industry dictating what kind of line someone should have. I hope that makes sense.

**DR. HUDAK:** Dr. Nelson.

**DR. NELSON:** Yeah, just a quick comment on this idea of limiting this decision to this context, this trial, this population. As you recall in the background document, and we gave you an example of where this issue came up before, and I'm just making the point that I would not consider any decision here to extend to that population. That was a trial where it was a four-hour infusion every day for two weeks and then six months off and then another four-hour infusion every day for two weeks at six months.

And that trial was actually conducted in 104 sites and only 16 sites used central catheters and these were mainly PICC lines. So, it was unnecessary for that population -- this was a type I diabetes population -- unnecessary to do just because they could conduct a trial on the other sites and the likes. In my mind, that is a useful counter example to say why the population and the context and the burden is very important.

I want to reassure people that, you know, extending this to other Duchenne trials is an open question that I will ask. But it's an open question in my mind about whether you can draw similarities between this and other populations.

I mean, I think that would be problematic and even if that was done, in my mind, there would still have to be a transparent process and so on and so forth. So, I do not anticipate that happening, I just want to reassure people. I don't! I think the immediate case would be a similar trial, similar product, similar infusion duration, frequency, et cetera. That would be the question that I would ask, limiting it to that specific set of facts.

**DR. HUDAK:** Amy.

**AMY CELENTO:** Amy Celento, representing pediatric patients here. I guess the point of the devil you know versus the devil you don't is really what we're dealing with. And we've heard today the devil that these kids know and it just seems completely unacceptable.

I will say that my experience with ports in the thalassemia community, for children who have highly inaccessible or very small veins, is that I know a number of children who have ended up in the ICU because of port complications, and multiple times. So I think highlighting the risk is incredible appropriate. I will say that if children are being seen every week, making extraordinary efforts to go to UCLA, there, hopefully, will be very careful attention paid to those patients and what's going on. And certainly, hopefully, any sort of concerns would be flagged very early.

But just in terms of understanding what these patients are going through, they're incredibly brave. And we've talked about this in other ethic sub-committees, the pressure that an orphan community feels, a patient feels to continue on in a trial that's incredible difficult. Clearly, we've seen that today and I commend them. But I also can say that I wouldn't want any child to be subjected to what they're experiencing week after week.

**DR. HUDAK:** Alright. I guess not seeing anybody else with questions I'm assuming that everybody has reached an answer to question one. Skip?

## **COMMITTEE DISCUSSION AND VOTE**

**DR. NELSON:** I just want to remind people of the procedure, is you have voting buttons on your microphones. In your case Richard, just take that from Sam, he's

non-voting. Just take it from him. And basically, the question that is posed to you, you vote and then we record that. And we'll go around the room and hear from each individual about the why. Since we'll have that discussion question, just in the interest of time, you don't have to necessarily answer question two in describing why you answered question one the way you did, because you'll have plenty of opportunity to elaborate in the discussion question.

That's the procedure and so since I see them scurrying over around the IT side to get that set up, I'm not sure at what point we'll get the signal that they're ready to record the vote. But wait till we get that signal. In the mean time we can --

**DR. HUDAK:** Meditate --

**DR NELSON:** Meditate or do whatever -- oh, we're ready, oh, --

**DR. HUDAK:** We're ready.

**DR. NELSON:** Oh, we're ready --

**DR. MOON:** Mark, I got a question, am I a voting member?

**DR. NELSON:** Yes. And basically, you'll be asked on the phone what your vote is once we have the recording here. And my suggestion is that Mark will ask you your vote first so that you're not -- unless you're looking on the web and not unduly influenced by the vote of the other members.

**DR. MOON:** Fair enough.

**DR. HUDAK:** Dr. Fost.

**DR. FOST:** Yeah, we've only heard from people who seemed to be inclined to yes. Before I vote, if there's somebody in the room or on the committee who's likely to vote no, I would like to hear their reasons; because maybe there's

something I haven't thought of. So, if there's any no votes, I'd like to hear about that before I vote.

**DR. NELSON:** Norm, you're suggesting that information would change your mind. I've never known that to be the case with you.

**DR. HUDAK:** Dr. Cunningham.

**DR. CUNNINGHAM:** I'm Melody Cunningham. I just didn't speak up because I thought that Steve Joffe and Doug Diekema said exactly, you know, what I thought. And based on my experience with port-a-caths in HEM/ONC patients, pain in my palliative care patients and multiple IV sticks, as well as hearing from the families and reading through the data, I'm in complete agreement.

**DR. HUDAK:** Okay, so we will do the vote. I will take Dr. Nelson's suggestion and take an oral vote from you Dr. Moon.

**DR. MOON:** I vote uh ---

**DR. NELSON:** Oh, no, take it after everyone has voted, but before Dr. Moon knows everyone's vote.

**DR. HUDAK:** Okay. Well I wasn't going to tell him what the vote was.

**DR. NELSON:** Otherwise he has the undue influence on everyone else.

**DR. MOON:** Fair enough.

**DR. HUDAK:** Okay so press the yes button if you think that there are circumstances in which an indwelling central venous access device should be allowed in this ESSENCE clinical trial. And press no if you think there are no circumstances that would allow that. Please vote. So we'll display the vote, but not say what it is, and then ask Dr. Moon for his vote. You may display it.

**DR. NELSON:** Surgeons are not easily influenced by the opinions of non-surgeons, generally in my experience. Sorry Dr. Moon but it's an ICU --

**DR. MOON:** My wife is a non-surgeon and she has a lot of influence, so.

**DR. HUDAK:** All right, so Dr. Moon you may vote now.

**DR. MOON:** Yes. I'm going to vote yes.

**DR. HUDAK:** So the vote is 14 yes, zero abstain, and zero no. That's pretty – that's pretty compelling, I would say.

Let me ask a procedural question. We will go around the room now and first, everybody can have the opportunity to say why they voted how they voted. Let's see, where should we start? Dr. Kryscio, why don't we start with you.

**DR. KRYSICIO:** Okay, thank you. Of course, I voted yes. I'm the sole biostatistician, non-medical person who treats patients on the committee. I think by approving this it will help with the trial, and I was impressed by the testimony given by the UCLA IRB.

**MS. CELENTO:** Amy Celento. My vote was yes. Just referencing back to my prior comments in terms of the pain and suffering that patients are enduring now to participate in a clinical trial that can hopefully help their life as well as the lives of others in the community. And I think there's just extraordinary pressure to endure pain and suffering every single week and I'd like to see that pain and suffering alleviated, even knowing the risks that exists in terms of having port-a-caths.

**DR. FOST:** Norm Fost. I voted yes. The main reason is that I think the ethical consideration should be paramount. And in this case, we're fortunate in that the regulation requires us to look at the ethical considerations and pretty much only that.

And the ethics seems to me not to be a complicated ethical issue.

You have a terrible disease, very reasonable trial that has a reasonable prospect of benefit, even if only a 67 percent prospect of benefit for some children. And the risks of the trial, the main risks, seems to me are the venipunctures and all the physical suffering and the emotional suffering that comes with that. And that the port-a-cath, therefore, is the most effective way of minimizing those risks, and the small risks of the port-a-cath more than justifies that.

**DR. LEVINE:** Rod Levine. I think offering a port at any time of the study, even at the beginning is humane and ethical, so I voted yes.

**DR. BIRZESCU:** Maria Birzescu. I'm an anesthesiologist and I find that there is a lot of suffering in pursuing peripheral IV access in a patient population that has known difficult situation with peripheral IV access. And I think that a port-a-cath is a standard of care in this context, so that's why I voted yes.

**DR. HOEHN:** Sarah Hoehn. I voted yes, not because I thought there was such amazing evidence or support that there is a direct benefit, but more from the palliative care perspective of just minimizing suffering, and quality of life. And respecting the families, that they know best in terms of what their child needs.

I would certainly support it at the beginning of the placement. I think some of the people suggested doing it at the first time of the muscle biopsy to minimize the anesthetic risk. And I do think that the analogy people made between this and cancer, whereas with the cancer you get it on day two and nobody asks, and that's all within the context of a clinical trial. Somehow, this has been treated a little bit differently. But that's a long answer, but yes.

**DR. HUDAK:** And you've elaborated into question two already.

**DR. WHITE:** I voted yes. Michael White. I tried to argue my way into the reasoning behind this being a placebo-controlled trial to come up with some way we can do it without using placebo to obviate the need for a central line in the placebo group, and I can't. I think you presented good enough data to support the idea that this can only be done in a placebo-controlled trial.

As such, I would have to say on the basis of respect for persons' justice, beneficence, the port, the option of using a port, clearly is better than proceeding with continued attempts of putting IVs in a population of subjects that are likely to have a deterioration and your ability to obtain access in that fashion.

**DR. HUDAK:** As Chair I don't get a vote, but I think that my vote, my reasoning would be able to be divined. I'd also like to echo back to a point that was made, that this decision would still be the same even though I have great therapeutic equipoise about this treatment.

**DR. JOFFE:** Steve Joffe here. So I also voted yes. First, I fully accept and endorse the need for a placebo-controlled trial, so that means maintaining the blind, which is what sort of gets us in the predicament we're in. And I believe, as I said earlier, if you're going to be requiring 96 weeks of weekly infusions, the standard of care is the offer of an indwelling venous access device. And so, to withhold that offer from patients and families, I think is cruel and unusual punishment. I think amending the protocol to be able to make that offer is really core to being able to do this in an ethical way.

**DR. SAYEJ:** This is Wael Sayej. I voted yes, for many reasons. As Mrs.

Buller said, this is a no-brainer to alleviate the suffering that her son was going through. And for any -- any clinical trial, for a rare disease that is progressive, and with a rare medication that does not have any other alternatives, I say this is a no-brainer.

If it was a different medication where there are ten, 15 different other competitors out there, and this one is being administered in a different way to the point that's it's causing more suffering, then it's a no-brainer to say no. But in this case, specifically, this -- while we don't know whether this medication is going to help or not, we don't have any other alternatives and the parents are looking for something that's going to help their kid. And their willing to take that chance.

As a physician and as a parent, if it were my kid I would do the same exact thing. I commend you and I appreciate the parents' statements out there. And I vote yes.

**DR. FOLEY:** Aileen Foley. I voted yes. And I think it's the ethical decision for this patient population and for this trial. And was expressed by Dr. Joffe, I feel badly we had to come to this point, but I understand in a placebo-controlled trial it's difficult to place a port-a-cath, but it's the right decision for this patient population. I also thank the testimony of the patients and the families and their bravery.

**DR. CUNNINGHAM:** I'm Melody Cunningham and I voted yes. As you probably knew before the vote because I don't play poker very well, but for all the reasons that I expressed before.

**DR. DIEKEMA:** I also voted yes, and have already pretty much stated my reasons. But they are similar to what other people have mentioned around the table. And most importantly, I think I actually see a long term indwelling catheter option as

minimizing risk compared to what's currently happening.

**DR. TURER:** Christy Turer. I think it is the ethical thing to do for minimizing pain and suffering. I commend the trial design of 96 weeks, particularly, given the preliminary data showing complete merging of the two trajectories over the first 12 weeks until it was un-blinded. I think it's absolutely critical to have this duration of a trial, so I commend you for doing that.

I would like to -- if I was designing this trial, or part of the sponsor's group, think about tracking not only the procedural factors, so the surgeon factors, regarding the outcomes with the ports, but also the patient factors, particularly metabolic health. These patients are on steroids which affect blood vessels. So, thinking about the health of the child, their blood sugar, their blood pressure, thinking about those things. Does vascular health play a role in the outcomes with these ports?

**DR. HUDAK:** Very good.

**DR. NELSON:** Cathy could you display question two so it's on the board.

**DR. MOON:** Can I make a comment?

**DR. NELSON:** Oh, go ahead Marc, sorry.

**DR. MOON:** I think the argument to alleviate the pain and suffering is very, very compelling. You know, when I was describing the risks of a port-a-cath, I completely forgot to talk about the pain and suffering and the risks of continually blood drawing with the blood vessels -- the vein thrombosing in the arm can happen there, hematomas can happen there, all sorts of things. And the pain and suffering really, if you tell a person who is going to get a blood draw every week, he'll want a port if they're making their own decision, I think. That's it.

**DR. HUDAK:** Okay. Thanks. So, we have time to move on to question two. And perhaps, this might have a very clear and lucid discussion on this, so we'll go through it.

These are the following four issues, let's look at them to see if we need to break them down in each one, or whether or not an answer would be needed.

The first one has to do with the choice and timing of placement be left at the discretion of the study site investigator. Should the protocol include criteria for deciding, when a participant has difficulties such that the use may be appropriate? If the protocol should include such criteria, what type of criteria ought to be specified? And how should the burden of undergoing multiple failed attempts? I think, some answers may address all these questions at once.

**DR. FOST:** A point of order I think if there were, hypothetically, unanimity on number one, two, three and four become unnecessary. Two, three and four are only answerable if the answer is no to number one.

**DR. HUDAK:** We can start a discussion I think, start specifically on A and then if your answer takes care of B, C, and D that takes care of it.

**DR. SAYEJ:** I'll start the discussion if that's okay.

**DR. HUDAK:** Please. Dr. Sayej for the record.

**DR. SAYEJ:** This is Wael Sayej. I definitely think that the choice and time of the placement should be up to the principal investigator and the parents. They should have some autonomy in the decision-making process with. Again, following the principles of informed consent will ensure that everyone is well aware of the risks and benefits of doing a port-a-cath or not.

Also, now if we look at this in the other direction, where a parent does not want a port-a-cath. And you, as a principal investigator, have to make a decision whether you will proceed with treating this child who needs this medication, or who's on trial for this medication. How much are you going to allow the nurses in terms of doing three, four, five needle sticks every time this child comes in?

Will the principal investigator have the -- I don't want to say power or authority, but -- have the capability of saying enough is enough? We can't keep going with this. Or even the sponsor, we can't keep going with this and we have to decide on whether we're going to continue this kid on the medication or not. Again, this is just playing devil's advocate trying to look at it from the other direction.

But I think the parents and the principal investigator, or the physician in charge of treating the child, should have a say in when to put in the port-a-cath, what kind of port-a-cath, in conjunction with communications with the surgeons. But at the same time, we need to have some other guidelines and criteria for those who decide not to go with the port-a-cath, and what does that mean.

**DR. HUDAK:** Dr. Joffe had his hand up first.

**DR. JOFFE:** I endorse the spirit of A. I would actually change the language to left to the discretion of the participant and parents in consultation with the site investigator or physician and surgeon. I think ultimately, the decision really rest with the patients and their families about when do to this.

I would not endorse writing into the protocol, minimal criteria of failed to get accessed this many times or some minimum number. I think it is something that can be decided upfront at the start before a kid gets their first infusion. I think placing it at

the time of that first muscle biopsy, if that's the decision, makes a lot of sense. But basically, I think this is a decision that ought to be in the hands of the families and patients once they have heard the information from the investigators, from the surgeons. And, again, would not endorse placing more stringent conditions.

I do hear your concern about if things are going very badly over the course of a number of infusion, a decision has been made not to put in a device. And then many weeks in, it's very difficult and a child is suffering. I suspect very few families are going to be in this situation. In other words, very few families would want to continue with the IV access once things start to go that badly.

But I do hear the concern that if for some reason a family wanted to go in that direction, might there be a situation where the investigator, the nurses would say we can't continue like this. I can envision that possibility but, for all intents and purposes, I think that the primary decision makers here ought to be patients and families.

**DR. HUDAK:** Dr. White.

**DR. WHITE:** I think it's become abundantly clear that the subjects in these studies are likely to have deterioration and the ability to start lines. And I think it should be at the discretion of the family and the physician investigator to consider starting these as early as possible, and with any other sedative procedures in order to avoid destroying what venous access might become necessary later in life when that port is gone. And I think that should be part of the discussion at the very start.

**DR. HUDAK:** Dr. Fost

**DR. FOST:** I agree with Steve's comment. The decision should be parents and investigators discussing it together. Second, voting for number one, amended in that

way. I don't think we need to worry about changing the language. I think from previous experience with this committee -- correct me if I'm wrong, Skip, but -- if in our discussion and comments this is an endorsed theme, I think that's helpful to you. It doesn't need to be, we don't need to re-word that.

Second, I just want to say that voting in favor of that doesn't require that there be a port. If for some reason a child is phobic about a port for some reason -- I can't imagine what the reason would be, but -- it allows for at least starting out with venipunctures and seeing how it goes and changing later, or continuing if it's going well as it might in some children.

And the third thing I wanted to say is, these micromanagement decisions about the qualifications of the port provider, that's ethically very important. But that seems to me part of what IRBs do in general is they require investigators, who are going to do procedures, to submit credentials to the IRB. I think that PI should have to provide some assurance to the IRB that only qualified -- interns won't be doing this -- that only qualified experienced surgeons will be doing it. That is, I think that's very important, but I don't think the FDA needs to micromanage that.

**DR MOON:** Yeah. I agree with not actually putting numbers and things on requirement. Just saying that an experienced central line access surgeon -- and it doesn't, you know, it doesn't specifically have to be a surgeon, it could be interventional radiologist. But an experienced central line placement individual must be the surgeon -- implanter.

**DR. HUDAK:** Dr. Nelson.

**DR. NELSON:** I just want to make sure I've heard a few aspects correctly.

So, although I've heard some discussion about risk minimization in terms of potential choice for proactive placement of a port-a-cath or other device at the time of muscle biopsy, what I'm hearing, at least, from several people that, that would not be an absolute requirement. That, in fact, a parent in consultation with their advisors could make a decision to wait. And then should that occur, you would be accepting the risk of a potential additional anesthetic for the placement of a port at another time, other than when the muscles biopsies are being performed. I mean, that's what I've heard.

The choice of the device, well let me frame a question around that after. I agree with what Norm said about locals IRBs, but I might also point out that the sponsor has a responsibility to make sure the people that are, in fact, conducting the procedure within the trial are doing that according to an appropriate standard. So, they also have that obligation and that's in communication, obviously, with the site PI and so on and so forth. So, there are other aspects of that that would assure appropriate expertise, independent of the IRB or in addition to the IRB.

But I am curious about the device issue. I mean, I hear what Sarah Hoehn said about the potential that a port-a-cath might not be the best device. But I certainly heard that that would, most of the time, be the preferential device.

I guess my question is, is it adequate in the protocol to just leave it to the discretion of the choice of device, or would one word something, which often happens in a protocol, to say this is what ought to be used unless there's a reason to use another device, blah, blah, blah, something like that. I'm just curious about that particular issue, given the discussions of port-a-caths versus other devices and the comments that Dr. Moon made about his preference for port-a-caths. It would be helpful to hear some

discussion on that issue.

**DR. HUDAK:** Dr. Cunningham first.

**DR. CUNNINGHAM:** Melody Cunningham, and I'll disclose a bias; I'm married to a vascular surgeon and so we talk about lines frequently. And if he were here he would definitely have a strong bias for a port and feels that PICC lines have significantly more complications at least in his experience, not that it's always borne out in literature that we read.

I think that if the choice is left open -- so first back to your question, Skip. I think to recommend that a port-a-cath would be first choice, unless there were other mitigating circumstances, makes sense from my standpoint. And then if other devices are chosen, to make sure that it's kept track of, you know, how often does those -- whatever the device is -- need to be changed? What complications are there?

So, that perhaps in moving down the road in overall four years, we might get more data and might really push towards, you know, one versus the other. I mean, the midline catheter is in there and I imagine that there might be some very mitigating circumstances why you would use something that's so short term. But I almost, in my mind, would take that one off of the list of possibilities, or perhaps nearly off the list of possibilities.

**DR. SAYEJ:** I just want to clarify something. This is Wael Sayej again. While we prefer -- since we approved this and everyone agreed, while we prefer that the patients get their central lines placed at the time of their muscle biopsies, I don't think we can make it mandatory as part of the protocol to do that. And that's why I ask the question, what if the parents didn't want the port-a-cath to start with. They should have

the option down the line to have the port-a-cath placed. And the physician should have some say, as well, in terms of saying that we need to move on with that.

With regards to what type of port-a-cath or central line, I definitely agree with Dr. Cunningham that PICC lines don't last as long. There's a high risk of malfunction and clotting. The central lines also have a higher risk of infection, compared to port-a-caths, which are hidden underneath the skin and only access when you need to. And therefore, there's less risk of infections.

So, therefore, my suggestion is to put it in the language where we recommend the port-a-cath unless the principal investigator or the surgeon thinks that there's an alternative option that would be better for the patient, so patient specific treatment.

**DR. HUDAK:** Dr. Maldonado.

**DR. MALDONADO:** I just want to ask a question. Port-a-cath is a registered Mark, so it's a trademark. Can the government or the advising committee recommend you should use this particular trademark?

**DR. HUDAK:** Does anybody have the --

**DR. WHITE:** I think the other term is an indwelling catheter, is the generic term. And maybe we should correct port-a-cath with indwelling catheter.

**DR. NELSON:** We will consult with the Center for Devices to make sure that the term we're using, that captures something that's under the skin that can be accessed, that's not penetrating the skin before it's accessed, that we're using a term that is not trademark specific, if that would satisfy you Sam.

**DR. MALDONADO:** No, not me at all. I don't care, it's not part of my

company anyway. But I've been hearing these and I know this is a trademark, so.

**DR. NELSON:** There are circumstances where the FDA has recommended certain things if there's only one of them, and I just don't know if there are more than one of them. So, we will find out if there are more than one of them and we will use a term that does not show preferential bias towards any particular manufacturer of indwelling catheter that allows access. We will do that.

**DR. HUDAK:** Dr. Hoehn.

**DR. HOEHN:** Sarah Hoehn. I just want to say that I certainly agree that there should be some language that this under the skin port-like type, indwelling catheter, would be first choice. But I just think we should allow for the possibility of other options.

And it's more from clinical experience. I worked with families who, at some periods of time, were very resistant and didn't want a port placed, whereas, a PICC line to a family was a lot less invasive. And I certainly think the data supports that port placement being the safest option. But I would hate for somebody to not be able to do it if, for some reason, they wanted a different type of line; or as I mentioned earlier if there was some anatomical contraindication.

But I certainly think there can be language in there saying that. You know, something that is completely covered up and under the skin. An enclosed device system is the safest first choice option.

**DR. HUDAK:** Dr. White.

**DR. WHITE:** There's a paper from Washington University in 2006, that refers to it as implantable vascular access devices (ports). That seems like a reasonable

language.

**DR. HUDAK:** Dr. Diekema.

**DR. DIEKEMA:** Yeah, I was going to say exactly the same thing, the source of all wisdom, Wikipedia, cites 11 brands of totally implantable vascular devices, so.

**DR HUDAK:** Dr. Cunningham.

**DR. CUNNINGHAM:** Melody Cunningham. While we're on the topic of the device; so, I don't know if we should discuss the possibility of double-lumen catheters, which might allow drawing of those pharmacokinetic studies through one of the lumens as well as infusion through another. It might mitigate some more of the pain and IV sticks.

**DR. NELSON:** If I could channel my eyes, maybe Sarah was going to talk about this. The first question I would ask is the port -- you know, just because they're separate doesn't mean that if something goes down one line and you draw blood up the other that you don't get contamination and cross contamination. You know, you'd really have to study that to see what the timing is and the relationship to the infusion and to the extent to which that would occur.

And also, at least I was trained, that the risk of infection is directly related to the number of ports; and so, you're doubling what might be a small risk. That's the tradeoff. I guess I stepped out of my FDA role into my ICU PICU role, sorry about that. But I guess if Sarah wants to expand on it, she can.

**DR. HOEHN:** Sarah Hoehn. No. I was just going to say, my first thought was, oh, my gosh stay out of it. I think it should be a single lumen, minimal risk, and I

don't think we should we get into it. But I don't think we should leave an option for a double-lumen broviac.

And just thinking about other, you know, triple-lumen lines and things like that, it doesn't necessarily help you with pharmacokinetics. And it certainly would -- there's good data it would increase the risks. I think we should stay out of it and keep the language to the implantable vascular access device, which by definition is one port.

**DR. CUNNINGHAM:** And I was just playing devil's advocate because I do know that they have more complications, but I could anticipate that this will come up at some point. And if you can give incompatible medications through those two lumens, I think you probably could get accurate pharmacokinetic data. But I agree, I don't think that it's the right choice, but I think if we don't talk about it, it may come up in other clinical context.

**DR. HUDAK:** Has anyone not had a chance to speak on this set of questions? Who wants to speak?

Let me summarize what I've heard. I think I've heard unanimously that the discussion about the choice in timing of placement of appropriate central venous access device should be a discussion between the family, the site investigator, and the surgeon. That the protocol should not be restrictive about any of those issues, should not be restrictive about the timing issue and that it should allow simultaneous placement at the time of the muscle biopsy, to take advantage of a single sedation anesthesia procedure. But that it's obligatory at that time, that it can be done at some other time.

And should the decision come up at a later time, that it needs to be done, that nobody indicated that there should be particular criteria that we should define; that,

that should, again, be left up to the discussion between the family, the investigator on that issue. Is that a fair capitulation of thoughts?

And that with respect to the device itself, then it's going to be stated somewhere in the revised protocol the advantages of the indwelling subcutaneous device compared to others in terms of risk. But not, again, be restrictive against others should the clinical situation so indicate that an alternative device is preferable, at least, in a transient period of time. So, that being a fair summary? Yes? Dr. Foley.

**DR. FOLEY:** I just want to highlight, you probably said it before, but that children should be assenting to the procedure.

**DR. HUDAK:** Absolutely, I'm sorry, yes, absolutely for sure. Okay. Thank you. Make that explicit. Dr. Diekema.

**DR. DIEKEMA:** Although it's not specifically here, there was a strong sentiment that the consent form needs to be very straight forward about the risks of whatever catheters might be allowable.

**DR. HUDAK:** Thank you. That having been said is Dr. -- you've said it so well that once we decide on A, that discussions of B, C, and D seem to be moot. Does everybody agree with that? Dr. Nelson.

**DR. NELSON:** No. I agree. And I think the intent was to write them in an order by which they were logical. And if, in fact, you decided there shouldn't be specific criteria, then it's true that B, C, -- I mean D, to some extent, is the overall background of the discussion. So, I agree with that.

In my own mind -- and this is not something I'm asking advice for. But as I mentioned procedurally, if the protocol is modified to include this option as a

discretionary choice, it's possible that a local site may decide to put into place, for example, some of the criteria that UCLA -- or they may decide, based on this session, to not use those criteria, that's up to them. But the point is, I would want to write a protocol, and I think the sponsor would want to write a protocol, that if a local site did decide to put in some criteria, that in fact that doesn't require a protocol revision.

And so, there's a challenge to how to word that so that there can be some flexibility at the local site based on their own particular views, if you will, about whether there ought to be criteria; but not necessarily then require going back through all the other IRBs and the like. That's something that we'll give some thought to. I'm just thinking about how one would word that section.

**DR. HUDAK:** I think the sense of the committee that I got was that we wanted to make sure the protocol read in such a way that the local IRBs and the local investigators had a lot of flexibility on that.

**DR. NELSON:** Right.

**DR. HUDAK:** Any other comments. So, Dr. Nelson barring a question three appearing on the slide --

**DR. NELSON:** No, we don't have a question three. And again I just want to reiterate the process here. And so basically the FDA Commissioner makes a determination. This is not a HHS-funded or conducted study, so we don't go through the second step of the secretary of HHS of having to then make a decision; so, it's a simpler process.

We need to put these materials together and brief the new FDA Commissioner, Dr. Gottlieb, on this issue. And I hope we can do that in an expeditious

fashion. But I'm also cognizant of all the other demands on his time. I mean, I will make a promise to everyone here that we'll do our best to get that done quickly, but I'm not going to promise an exact timeframe for that determination to be made.

It will be written as a letter to UCLA and to Sarepta, they will be the first to know. And then it will be posted publicly on the advisory committee website as well as to the docket. At that point, everyone will know what that determination has been, so that's the process.

I think this has been a fascinating and interesting discussion and I thank everyone for their participation. As I said, both the Duchenne community, the UCLA folks, Sarepta and everyone around the table, I think it's been an important discussion. There's a lot of subsequent thinking about this process that perhaps can emerge out of this, which I'm happy to engage in separate from this particular protocol, about the ways these things are dealt with within our regulatory system.

**DR. HUDAK:** I'd like to close and say, also echoing Skip, that the members of the committee really appreciate the expertise and the professionalism of everybody who presented today, including families and children that are being treated. This gave us, I think, a great deal of additional insight into this issue and made our way I think very straightforward. With that, I think we'll close the meeting. Thank you.

**[MEETING ADJOURNED]**