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**Acute Ischemic Stroke Medical Devices Trials Workshop (10/06/2015)**

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FOOD AND DRUG ADMINISTRATION (FDA)  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

ACUTE ISCHEMIC STROKE  
MEDICAL DEVICES TRIALS WORKSHOP

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**A P P E A R A N C E S**

Michael Hill, M.D., University of Calgary

Martin Ho, PhD, CDRH, FDA

Mary Lee Jensen, M.D., University of Virginia

Pooja Khatri, M.D., University of Cincinnati

Daniel Krainak, PhD, CDRH, FDA

Viveca Livezey, M.D., CDRH, FDA

Carlos Peña, PhD, CDRH, FDA

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P R O C E E D I N G S

INTRODUCTION TO WORKSHOP

DR. JENSEN: Okay, if everyone could take their seats, please, we'll get started.

Thank you. So, good afternoon, and thank you all very much for taking time to come to the Acute Ischemic Stroke Medical Devices Trials workshop. I'm Lee Jensen. I'll be one of the moderators for the session. And Jamie Waterhouse, who's the project manager, asked me just to speak a little bit about why this workshop is important. And I think we all know why it's important, because stroke is a very important disease process. I mean, it's ubiquitous. It affects all ages, ethnic groups, sexes and it takes a really physical and emotional and mental toll on our patients and their families, in addition to the economic burden not only on families but also society as a whole. So that's why we're here. We're here to help patients by figuring out the best way to examine this disease process to get the answers to the questions that we need.

She also asked me just to mention a little bit about stroke therapy over the years. And as I look at this group, there are a lot of people out there who actually did all of these trials, started all of these trials. But for those of you who are younger, you have to recognize that there has been an incredible explosion of information over the last 20 years in terms of stroke information and therapies because before 1996, pretty much what we did when a patient came in with a stroke was do medical management and send them to rehab. But everything changed with the NINDS trial, when patients actually were able to be offered a therapy within the first three hours of the onset of stroke in the form of IV t-PA.

But at the same time, those of us who were in the interventional system were busy looking at how to deliver drug intra-arterially. And out of that came two trials, the PROACT and the PROACT II trial, which showed that, yes, indeed, you could in certain patients

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affect by recanalization of the clot a good outcome. And at the same time, in Cincinnati, that group and their colleagues were busy looking at combined therapies, the so-called bridging trials of IMS I and IMS II. And in that particular case, also using sort of a mechanical device, which is the picture you see here, which is the EKOS catheter, to perform not only therapeutic delivery of drug but also ultrasound.

Things really took off, though, when mechanical devices to extract clot came onto the market. And Dr. Peña is going to talk more about that in a moment, with the first one being the MERCI device that was approved in 2004, followed by a suction thrombectomy device, Penumbra device, in 2008. But it wasn't until 2012 where we really had the development of the current generation of devices, the so-called stentriever.

Now, one of the really important things that was going on at the same time was the IMS III trial, which was an IV versus IV bridging IA therapy. And when this trial first started, a lot of patients were being treated with intra-arterial thrombolysis. And as the trial went on, devices were added. And everybody thought that this was going to show that patients who had clots extracted would do better than patients who had just intravenous therapy alone.

Unfortunately, the trial was stopped in 2012 due to futility because there was no difference in the achievement of the endpoints between the two groups. And this was a really great blow to the interventional team and to stroke therapy, people interested in stroke therapy as a whole.

But one of the things that was noticed that patients who had large vessel occlusions seen on CTA during this trial seemed to do better than just the IV therapy group. And so, from this came the idea that I think those of us in the endovascular field felt very certain about, was extraction of large clots very early on was going to be better than just intravenous therapy. Unfortunately, two other trials at the same time were negative. They

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were all published at the same time as IMS III, MR RESCUE and SYNTHESIS. And it really did look like intra-arterial therapies were going to just go by the wayside. But key learning points came out of these trials. And one was that imaging was really important to confirm that the patient had a large vessel occlusion and that we needed to exclude patients who already had large infarct cores. And we needed to speed things up. We needed to be faster and we needed to use the newest devices.

So in 2015, we were very fortunate in a very short period of time, over three months, there were four trials that came out, MR CLEAN, ESCAPE, EXTEND-IA and SWIFT PRIME, all of which agreed with what I think we all knew intuitively but couldn't prove, was that extraction of large vessel occlusions early on was better than intravenous or standard medical therapy. And if we just looked at this trial summaries here and look at the different between those where there was no imaging required, that would be IMS III and MR RESCUE, to look at a large vessel occlusion, versus these four new trials and the fact that we knew what we were going to be attacking and that we were using primarily new devices, i.e., stentrievors, that the outcomes were much better in the treatment arm, the intra-arterial treatment arm.

So my esteemed speakers after me will go into this more thoroughly. But this was really the beginning of a new push to go after large vessel occlusions intra-arterially and as quickly as possible. So the purpose of this workshop is to obtain feedback from the stakeholders in stroke on the scientific and clinical considerations associated with the development of medical device trials going forward for the treatment of patients with acute ischemic stroke. And we need you to help the FDA to develop an overall strategy to promote these advances in the technology while maintaining appropriate protection of our patients and to inform the guidance on trial design and PMA submission for evaluating these devices.

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So that's your charge today. We hope that when we leave this workshop, we will have a better idea of how to design these trials. And I'd like to say thank you to the FDA CDRH leadership and staff, particularly Dr. Peña, Dr. Ho, Ms. Waterhouse, all of the speakers and moderators that will be coming up onto the podium and working with you today on the workshops, and again to all of you for taking very valuable time to participate in this workshop. Thank you very much. Oh, and next is going to be Dr. Carlos Peña, talking about the history of stroke devices.

**HISTORY OF STROKE DEVICES**

DR. PEÑA: So I think you've given a very nice history of the history. I might actually not have such a long talk. But my name is Carlos Peña. I'm the director for the Division of Neurological and Physical Medicine Devices. And when we planned this event, we were thinking of, you know, a brief workshop in the afternoon, some attendees. And it really turned out to be an amazing attendance to this meeting. So I'm really happy to see so many people, some faces I know, some faces are new. And I think it really speaks to the investment that you are making in this area. The Division of Neurological and Physical Medicine Devices is one of the newest divisions in the Office of Device Evaluation at the Center for Devices. And I think that also peaks to the investment of the agency in this area.

We're here today to talk about stroke devices and the ideas generated during this workshop -- let me go to the full screen here. The ideas generated during this workshop will facilitate further development of guidance that we have. We have an existing guidance. But we also see opportunities to enhance that guidance to promote this technology sector and speed development of this area. So I have some history. But I also have some regulatory background for you to set the stage and to have a more informative discussion with a

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regulatory background that I think you need going into the sessions.

So our primary vision is to bring to patients greater accessibility to high quality, and I'll say the safe and effective medical devices of public health importance and be first in the world in this. We also want to speed product development and give the public accurate science-based information. New interventional devices have been and continue to evolve over the past several years. I think there was one study reported in very recent literature, in the *Journal of Neurosurgery*, by Munich, et al., where they noted a 1994 study of thrombolysis mechanical clot disruption with microcatheter and wire manipulation was used for the treatment of stroke. So there's been a lot of development since that time. And although drug therapy has traditionally been the approach to treat stroke, the past several years has given rise to neurothrombectomy devices also playing a role in treating patients.

Now, the progress in neurologic devices has played a role in medical device review and the process is challenging. I will be the first to admit it. These are not easy questions that we have when we see submissions come before us, especially when you're trying to balance the need of the patients, considering the mortality and the morbidity, the evolving device technology area, the importance of providing information to users of devices and the importance to protecting and promoting the public health. And these are all the types of the issues that the FDA has to deal with.

There are a number of decision points that we will -- I'll get to next. But they include medical device classification, benefit/risk assessment, predicate devices, if that is a path that is taken for the device in question, looking at valid scientific evidence, which can go from well-controlled, randomized, blinded studies to historical studies to other sources of information to make decisions and keeping in mind that we have to take the least burdensome

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approach for our sponsors. Takeaway messages are that during the research and development of a medical device, sponsors may approach FDA for guidance on the suitable design of a clinical or nonclinical study. And there are many factors that the Center for Devices considers during its review.

For some background, medical devices are classified into three -- one of three classes, including class one, two and three, with regulatory control or oversight increasing from class one to class three. So the device classification regulation defines that the regulatory requirements for a general device type. For example, most class one devices are exempt from submitting an application to FDA. And one example of a class one device is a mechanical wheelchair. Most class two devices require premarket notification. One example of a class two device, and it's the very focus of our workshop today, is neurothrombectomy devices. And most class three devices require premarket approval. An example of a class three device can be aneurysm-type devices that we have seen at the agency. And I will talk a little bit more about the requirements for each pathway.

But the main takeaway is that we provide oversight across the three classes of devices using tools known as general and special controls. And FDA tailors its regulatory requirements to any given device. And we focus on communicating to sponsors what they need to do to meet the regulatory requirements to bring their device to market. Another question that might arise during the discussions is when is clinical data needed? And so, typically for PMAs, almost always clinical data is needed. For de novo submissions, and I'll talk a little bit about that in just a sec, clinical data may be needed but may not always be needed. And for 510(k) submissions, clinical data is typically not needed, although there are cases where we have asked for clinical data for those submissions.

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So you're probably saying to yourself, Carlos, really, like there's some provisos. There's some, you know, guidelines. There's some clarifiers. How do we find out what really is needed? And the best way to do that is to come talk to FDA, come talk to the staff that we have in the division. And that's the best way to get feedback on the protocols, the regulatory requirements, the studies, the endpoints, the eligibility criteria, the informed consent documents. All of those details help us to help you guide your product to the marketplace. And I'll return to a little bit more about this shortly.

We have been engaged in neurological device development for some time. And me, as well as my predecessors, as well as the staff that's within the division, here I show you an array of products with neurological indications, beginning with neurothrombectomy devices. And we also show you several other neurological medical devices. The purpose is not to discuss with you the safety or effectiveness of individual devices, but share with you that each device went through a regulatory pathway that was in part tailored to the individual benefits and risks of the device.

So when the first device, we were talking about subject in a clinical study, that was a neurothrombectomy device, the MERCI study. And the very last set of devices that are generally cleared with nonclinical performance data, due to safety and effectiveness data of being established in prior submissions. Take-home messages that we continue to optimize our approach in reviewing devices, reducing the time and cost of the clinical trial enterprise and striking the right premarket and post-market balance between conducting an appropriate evaluation of neuro technologies while at the same time getting the products to patients who need them.

For the mechanical neurothrombectomy clot retrieval devices currently

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marketed, the first marketed product was the MERCI retriever. And each new clot retrieval device, a few shown here, have been reviewed for substantial equivalence under a 510(k) submission for the same intended use of revascularization within eight hours of acute ischemic stroke symptom onset in patients who were ineligible or who failed IV t-PA therapy.

As device technology has evolved for acute ischemic stroke, since the clearance of the first retriever we reviewed and cleared new clot retrieval devices and all have had the same intended use, but with slightly different technological characteristics and despite those differences, these devices were deemed to be substantially equivalent because there was no different safety and effectiveness questions raised. And I think I went through some of the 510(k) pathway in the prior slides. FDA and staff specifically in our division look very carefully at neurothrombectomy devices. And as are all our submissions for neurologic devices, we take -- we walk a very challenging walk and walk a very difficult line between protecting and promoting the public health with obtaining the right safety and effectiveness data before devices get to market.

As I mentioned, our division of neuro is one of the newest divisions in the Office of Device Evaluation. We also work with, and it's shown here on the second row, other offices, including the Office of Science and Engineering Laboratories to further understand the science to support making the most informed decisions, and that's abbreviated here as OSEL. We also work with compliance in evaluating medical devices and technologies already in the marketplace to make sure they do what they say they do and they do not harm patients and consumers. The office that specifically receives submissions from sponsors and investigators is here on the right side, the ODE, device evaluation. Right below that is shown seven divisions, for which neuro is one.

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FDA released draft guidance -- actually final guidance for neurothrombotic devices and then defined the sector as intended to retrieve or destroy blood clots in the cerebral neurovasculature by mechanical, laser or ultrasound technologies or a combination of technologies. This guidance was released in 2007. And considering the clinical research and development in this area, the recent publications of different studies and the promise of these types of technologies, FDA has convened this meeting today to further enhance its approach to the review of products and our guidance to sponsors and developers.

I am also a very, very big fan of transparency and public meetings are the best way to communicate our public meeting, as was illustrated with the position paper that was part of the documentation for this meeting. Over the past two years, we've planned a number of workshops, including brain/computer interfaces last year. Earlier this year, we hosted an advisory committee on aneurysm devices. Today, we have stroke. Next month, we have non-invasive brain stimulation and neuro diagnostics. And I think all these meetings are part of a process for making FDA more touchable to sponsors and developers but also sharing our approach and our current thinking and ways to improve and enhance that thinking about different technologies.

We have a very specific agreement for today to focus on what relates to the guidance. There were seven areas in the guidance that we have currently from 2007. I think the focus of the workshop today will be focusing more on the clinical topic areas, both clinical studies and measures of success. We have four specific topic areas, including clinical study design, clinical outcomes, patient imaging safety and statistical considerations, as well as registries. And this last topic is a new area for us, as we are trying to make sure we understand the scientific and clinical considerations in using registries for decision-making.

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So a few closing thoughts, and then I'll turn to my colleagues to walk us through a little bit of a statistical side of the house. First, these meetings do not happen on their own. And I'd like to thank FDA staff presenters this morning, moderators this afternoon -- actually presenters coming up, and moderators as well this afternoon, that engaged in this effort. This is not a one-person-show. But this is actually a team approach that includes people from within and outside the agency.

Secondly, I would encourage all stakeholders to engage in the discussions during the sessions. We do not want to just have one sector perspective. But we want to feel like all can participate and voice their opinions and their recommendations for discussion. And third, this is a very exciting field that presents challenges to the agency. I'm hoping, and I've got to say this, right, I'm hoping that you are all as smart as we think you are to help us address the scientific and clinical considerations in this area and moving forward to getting safe and effective devices to the marketplace. So I'll turn to the next presenter, Dr. Martin Ho.

[Applause.]

**STATISTICAL CONSIDERATIONS**

DR. HO: Thank you, Carlos, and thank you, Jamie. As Carlos mentioned, it's not -- I mean, this meeting is basically -- definitely a group effort, just as shown by Jamie's help. So good afternoon, everybody. My name is Martin Ho. I am the acting chief of therapeutic statistics branch two in Division of Biostatistics at CDRH. And I would like to thank my wonderful teams who are supporting this presentation.

As shown in your discussion -- you know, in our workshop's discussion paper, we've seen quite a few topics with a wide range. And given the time, I have chosen a few topics to highlight and hopefully I will show -- present you with some new materials for your

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consideration. I will first walk through some of the basic and general design considerations as applicable for any statistical effort in clinical trials, old and new. And then, I will discuss two unique and yet new challenges that we are facing as statistical reviewers. Then, at the end, we would like to show you a good story which is a statistician, you know, step up to the plate. We rise to the occasion and we found a very interesting and elegant method to answer to the challenges.

First, a general issue during the design issues for neurothrombectomy devices, it's extremely challenging for us to blind [inaudible] assignments of two arms. So therefore, we are trying our best to maintain the integrity of the study. And we have decided that a masked evaluation would be a good compromise in that department. But we are always looking for maximizing the level of masking that we can do that is at the same time feasible. And then, the second point that we want to say is statistical analysis plan is extremely important piece. And typically it would involve at least five components that's listed on the screen.

First and foremost, of course the well-defined and specific definition of endpoints and analysis populations are crucial and the sample size calculations and the assumptions made is that helps to justify and also to design the study so that if we can set up the study to succeed. Third, the type I error rate and multiplicity adjustment planning are also very important so that we will be able to control for the overall false positive rate. And missing data [inaudible] sensitivity analysis are very important tool, you know, in our toolbox so that we would know at the end. We don't need to argue or we don't need to have a dispute about how the missing data should be imputed. And if all these things are being prospectively specified, we would save a lot of efforts to try to reach a consensus about how to interpret the study conclusion. And finally, it's extremely important for us to assess the impact of the critical

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covariate.

Even with -- even if we are using two identify study protocols and tapping onto the same patient groups, we still would have come up with a slightly different study results because of the different mix of the patients and the subjects. So therefore, it is very important for us to understand how sensitive the study conclusion is regarding the distribution of the covariate. And the third point that I want to talk about is there is a discussion about whether we should adapt a respondent analysis, which is just classify the individual treatment success or failure or we should actually look at the ordinal categories of the individual patients that they have experienced. Since we are looking at the full spectrum of the categories, for example, modified ranking scales, if we are using all this information, we will be able to have more or higher power for us to detect the differences between the group. But at the same time, we are facing a challenge to try to have a clean and easy interpretation of the study results as the respondent analysis.

So in this workshop, we are looking forward to hearing your inputs about how we should handle this conflicting tradeoff between these two important endpoints. I want to say that the FDA has always been very eager to recommend using an ITT population method -- primary population for superiority trials. And if it is possible, we would like to stick as close as we can. For example, in the modified ITT population, we would consider inclusion of any subjects in whom treatment attempt was made. And per protocol, population are mostly considered as a secondary endpoint, secondary population. And if we are looking at non-inferiority trials, then we would look at both the ITT and the per protocol analysis results. It's because the conservative conclusions provided by ITT analysis was no longer true universally. So therefore, we would be important for us to look at both the ITT and PP population to make

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sure that they have a good consistency with each other. And if they have significant difference, then it's our job responsibility to figure out why.

Next, I would like to talk a little bit about the adaptive design, which has been an increasingly popular clinical trial design that we have reviewed. Here, we define adaptive design as a clinical trial design that allowed a modification of certain aspects of the clinical trial based on an interim result in a prospectively specified manner. So the key phrase that we have to remember about this is it should be adapt by design, not adapt on the fly. So here, that aspect of adaptation allows us to change -- for example, to increase sample size based on the interim result or we can enrich certain specific patient subgroups. For example, if over the course of the trials we find that a certain subgroup of the population responds very well to the treatment compared to the control, then the design would allow the allocation of the new patient would enroll into that specific subgroup. And it also allows for early stopping for success or futility.

And as I said, the good thing about this design is that it provides a certain level of freedom. But at the same time, it manages to maintain the type I error inflation. So therefore, it would be very useful for us to address any uncertainty at this design stage. And as we all know, when we do a sample size calculation, the assumptions that we made may not be realized when we are running the trials.

The second point about adaptive design that is very important is even -- I mean, even if we have the perfect plan for the trial, if we don't follow it, then it would be useless. So therefore, as the FDA look at the submissions using adaptive design trials, we would always look at how compliance the sponsor would be to follow the plan that they have prospectively specified. And if there is any deviation, we would also look into it in a very thoughtful manner.

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Next, I would like to talk a little bit about the interesting challenges that we are facing in reviewing the thrombectomy device. First is we all know that such strokes -- the strokes differ in sizes, regions, symptom onset or the prior IV t-PA uses. And since each clinical trial have their own specific mix of these different subgroups, sometimes it would be extremely difficult for us to make conclusion or to have enough evidence to submit -- to support our decision on whether the study would provide good evidence for labeling claim for a specific subgroup. For example, if there is a certain subgroup that has a very low prevalence -- for example, the posterior circulation stroke -- then in a typical clinical trial, we wouldn't be able to see too many of them. And therefore, the sparse number of stroke there in that specific subgroup would not be able to help us to decide whether we should include that into label or not.

So in here, we are proposing an approach which is to try to borrow strengths from the other subgroups to support the statistical significance tests for one specific subgroup. So if we are facing the challenge that I just mentioned, we have basically three different options to analyze the data. We can completely ignore the differences across subgroups and just pool them together as one big subgroup. The disadvantage of that is we cannot really tell the different treatment effects across these subgroups. And the second option is that we just analyze each of them separately. And that poses another challenge, which is if we power each subgroup separately, then the overall trial would be relatively huge. That would make the trial infeasible to conduct and we may actually not be able to help the patients by making the device accessible to them.

So here, we are facing kind of like an all or nothing scenario. And in order to meet that challenge, statisticians have come up with an idea called borrowing for statistical

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power. And basically it requires an assumption that we cannot -- we don't have an a priori expectation of the outcome of one subgroup compared to others. And this idea of borrowing will be discussed in a couple of slides.

The second challenge that we are facing is, just as the previous two speakers had mentioned, we had a very exciting year in 2015 in thrombectomy device. And then the question is, given the four significant positive results that were published, should we still assume that we didn't learn anything about thrombectomy devices and just do other clinical trials from scratch. And if not, then how are we going to be able to leverage these data in a rigorous, prospective manner to support regulatory decision. So the challenge of leveraging these data to support regulatory decision is because of their differences in the devices used, the inclusion/exclusion criteria, the imaging assessment and the concomitant therapies. So therefore, the use of the meta-analysis to support regulatory decision is quite challenging to us. So therefore, we would like to use the mechanism of borrowing to help leverage these data in a prospective study.

So why do we want to have -- to leverage the information from prior studies?

The main advantage is we can increase the position of a new clinical study and which in turn will reduce the sample size and the risk of exposure to the patients. And as I described in those previous two challenges, there are at least two ways to leverage these data. We can leverage across subgroup within a study, which, for example, we can borrow on the treatment effects across different subgroups. And we can also borrow across new and prior studies. We can look at the treatment effect across different studies or we can look at outcome of a treatment group -- for example, the historical control.

So in order to achieve that purpose, we would like to receive a pooling as a

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continuum scale. This is what I meant on the slide. On the one hand, we have no pooling, which is the status quo. We pretended that no -- I mean, these four studies did not happen. And we just evaluated the new study as this and there's no weight would be assigned to the historical data. And on the other extreme is complete pooling, which is the subjects in the historical study and the new study, they all carry the same weight. In other words, we just treat all the patients in both studies as if they were in the same trial. That is another extreme and we typically would not allow this to be used to support our regulatory consideration.

Now, here is the third way, which is the middle ground between the all or nothing, which I call borrowing or you can perceive it as a partial pooling. So simply speaking, borrowing strength from historical data means that we would use a weighted average of historical data and new data. And the weight of the historical data would depend on how similar the historical data is to the new data. And I would call this borrowing evidence basis because the more similar the new data is to the historical data, the more weight would be assigned to the historical data. In other words, we would be able to borrow more from the historical data.

So how are we going to be able to do this, the borrowing? We are using a model called Bayesian hierarchical model to facilitate this borrowing. And I want to emphasize that using a Bayesian hierarchical model is exactly the same as we are conducting traditional randomized trial. It's just the planning and analysis of the study result is different. So in other words, if we are using a Bayesian hierarchical model for borrowing, then it would still need to go through the same -- it has still to meet the same rigorous criteria of traditional RCT that we are so used to. And in other words, we need to prospectively specify the protocol and analysis planned and we also want to adjust the covariate, if appropriate, if the historical study has a bit

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different mix of patients from their new studies.

And in order to be able -- in order to leverage the Bayesian hierarchical models, we have to rely on certain assumptions. First is that exchangeability between trials or patient subgroups, which I will explain a bit more about what it means. And secondly, just like other good quality meta-analyses, access to patient-level data is crucial. And thirdly, I would like to emphasize the importance of using adaptive design in conjunction with the Bayesian hierarchical model to leverage the maximum amount of information from the prospective study. And finally, simulation is a very useful tool for us to evaluate the operating characteristics of the new trial design, including the power and the average number of patients recruited and what is the average time we would stop or terminate for success or failure.

So what do I mean by exchangeability? In order to make a new study to be exchangeable with the historical study, first, we have to choose a specific set of historical data that they are deemed to be similar with each other. And then, we want to -- we want to design a new study so that it would be very close in terms of designing conduct to the historical data or to the historical study that we intended to borrow from. The reason for that is we want to make sure that there is no -- okay. In other words, we want to make sure that there is no a priori expectation that any systematic differences exist among these trials. And in terms of exchangeability of patient subgroups, we are using the same criteria, which is we won't expect one specific patient subgroup to be better or worse than the others.

Finally, I would like to go through two very simple examples. Suppose we have a new clot retriever study that designed to be similar to one with historical data. And that trial is multicenter, prospective, open label trials. And it's they're comparing IV t-PA plus the device versus the IV t-PA alone. And as always, they are using mRS 90 as the outcome. And we are

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generating these two hypothetical examples based on the recently published study results. As you can see, this is the result of the study. And one thing I want to highlight is the odds ratio. As you can see, the new study, the odds ratio of new study is 2.14 compared to the H1 study of 2.56. And by borrowing the historical data, the new result is 2.13, which is the odds ratio is very close to the new study alone. But the advantage of borrowing can be shown by comparing the variance of these two situations. If the variance of using the new study alone is 0.33 versus the borrowed estimate, the variance is 0.26. and here, we are giving -- by borrowing, we are basically adding 27 percent of sample size boost to the borrowed analysis.

And the second example is instead of borrowing from one study, we borrowed from three. And you can see that the number of sample -- the size of sample size boost is 57 percent versus 27 percent. So the more information allows us to borrow from, the larger sample size we got.

In summary, we would like to encourage you to come talk to us early to decide -- to determine and to discuss your study design that you want to conduct. And then secondly, borrowing and adaptive design can be very helpful to address the issue of heterogeneity across and within studies. Leveraging data across and within studies, however, needs to be maintained -- needs to be keep under condition that the type I error rate is being checked. And all of that requires prospective planning of study so that we can make sure that they are exchangeable. And finally, the amount of borrowing depends on the similarity of the new data to the historical data. Thank you.

[Applause.]

LESSONS LEARNED FROM CLINICAL TRIALS IN ACUTE ISCHEMIC STROKE

DR. HILL: Okay. Thanks. Hello. Thank you very much for inviting me. My name

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is Michael Hill. I'm a neurologist from Calgary. So I have a little bit of a different perspective insofar as I'm north of the 49th and not regulated by the FDA. So I'll give you a perspective. You know, my perspective on the academic side of what's happened a little bit in stroke trials and comments related to regulation are, you know, to be construed in the sense that the FDA is essentially the preeminent health system regulator in the world.

And so, Health Canada, which is the body that I function under, is naturally significantly influenced by what happens at the FDA and they actually have an extensive reciprocal arrangement about sharing data. So we work together. So I was asked to make some comments about the evolution of clinical trials in stroke. And so, I'm going to -- some medical comments and some device comments. And I'll give you a perspective on what I think's been going on. So talk a little bit about history, devices, trial design and I'm going to end with some lessons which I hope will be provocative and get people thinking.

So this is the first thing to do, is to realize that obviously we look at the past to help us inform the future. And knowing what's happened in the past is very helpful. I think that history -- the history of how things have evolved often influences how things go. And the other thing to think about is that clinical trials are a relatively young science. It's not something that's new. And particularly in stroke, it has, as was mentioned in the introductory comments to this presentation, or the whole afternoon, that clinical trials in stroke have really, really taken off in the last 20 years. You know, the first big one in the cute stroke side was really the NINDS trial. That made a big impact on what's happening in stroke, the t-PA trial, and that was published in 1995. So we're not talking about a long period of time. And so, we're in a situation where things evolve.

The other thing I would say, just in my own experience, I had the -- and I would

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recommend this book to all of you. There's a book called The Emperor of All Maladies, and it's written by a fellow named Siddhartha Mukherjee, who's an oncology who works here in the United States. And he gives a terrific understanding of the evolution of how clinical trials worked in cancer, starting with the Dana Farber Institute and this kind of thing, but makes a really explicit point, which I picked up on in the book, which was that the regulation of trials also evolves, right?

The regulation of trials evolves and it evolves with the science so that the -- you know, when methotrexate and other first antimetabolites were developed for childhood leukemia, ALL, there wasn't the same kind of oversight that exists now for the development of drugs. And those, it's amazing when you read about what happened about, you know, developing a drug in a grungy basement in the bottom of a hospital in New York and then giving it to kids up on the sixth floor, so without the same kind of oversight. And so, I think all of us, me as an academic, we have to recognize that we coexist and it's terrific to be here. We coexist with the regulatory group. And they coexist with us. And so, the evolution's important. And so, this is what's happened with trials and it's happening in stroke.

So one of the things that's happened is of course we now are required to have proof to do stuff, right? We need proof of efficacy. And I hope that you all get a glass of beer tonight so you have proof. But now, we've evolved with clinical trials to a standard where we do need a randomized clinical trial to get approval. And usually, certainly on the drug side, the standard has been two randomized trials of similar design showing effectiveness in the population. So, and we need that or we can't move to that level. And here's the -- you know, here's the similar statute that exists in Canada. This is the Food and Drug Act in Canada. There's a similar statute in the United States. And it basically now with the regulation under

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that statute says that we have to have this. So we have a responsibility to provide proof to our society so that we can use new drugs and devices in a safe and effective way. And that's one of the things that obviously we have to recognize, that we are functioning under a legal environment, right?

Some of the first acute stroke trials -- I think stroke trials in general really started with prevention. But some of the acute stroke trials go back to the time I was in high school, 1980s, the early 1980s was hemodilution trials. And you know, these were done -- the first one there is 1989. That was published. But the first beginnings of them started a long time ago. They were all neutral or potentially frankly negative. And then, there was a whole series of developments about neuroprotection. And this evolved with the -- this was a bench-to-bedside story with the evolution of understanding of excitotoxicity and the belief that we could translate what was seen in the rodent models -- in particular, cell lines that we would be able to block excitotoxicity and then neuro-protect the brain.

And you know, I think Geoff Donnan did a -- or has published a relatively famous and oft-quoted article which is there were 1,026 molecules in that who were so-called neuro-protected, that were either started into phase two or they got to phase three and ultimately were canned because they were ineffective. And this, I think the NXY study was probably the largest expense in the culmination of the amount of money that pharma in particular put into this effort. Several hundreds of millions of dollars were spent on this development, only to ultimately have a trial which was neutral. And we can debate lots of the issues around why that was the case. But those were the randomized trials that were really happening in the 1990s in parallel with the evolution of thrombolysis. I participated in a big study recently which looked at albumin which also had very strong evidence for neuroprotection in the preclinical area. And

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again, we didn't find a result. And we can talk about some of the reasons why that might have been the case.

In thrombolysis, I think on the stroke side, we had similar misfortune to start with. And I think even looking at cardiology and other areas of medicine, we often start with a number of false starts before we get to the right spot. So on the right-hand side of the screen, we've got the thrombolysis trials. They started with streptokinase and the MAST-Europe and MAST-Italy trials and then the Australian streptokinase trial were all done without a dose finding study, using a cardiac dose of streptokinase, using a cardiac window of six hours. And most people were treated late. In the end, most people had a significant -- what we would now call a significant early change on the scan. And they were disasters, right? There were -- particularly when it was combined with aspirin in the MAST-D, which was a factorial designed trial, there was more hemorrhage. Yet, there was signal. So if you looked at the people who were treated very early on, streptokinase was effective.

And then, folks in the room here were involved with the development of t-PA on this side of the Atlantic. Dose finding trials were done. Safety trials were done, which led to the evolution of the NINDS-sponsored t-PA stroke trial, which is really to a very large extent led us to all being in the room today. So, and then there was ECASS-1 and II, ATLANTIS, ECASS-3, EPITHET and IST-3 was numerically the largest of the thrombolysis trials. And I think that the cumulative evidence, everyone agrees, in the right setting, t-PA is a very, very effective medicine for stroke. So we had this, you know, evolution over time on the medical side. And in parallel, we had a mimic on the device side, which was to try to figure out how to get arteries open. It was recognized early on that intravenous thrombolysis was not as effective when you had large vessel occlusion.

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And we started with PROACT II. Tony Furlan led that effort. It was sponsored by Abbott. And it was originally designed I think as a proof of concept trial. And it was in fact positive. It fit his primary endpoint, just  $p < 0.043$ , if everyone remembers. And then, when Abbott took it to the FDA, the FDA said, well, it's good. You're close. But you'd better do another one, right? And then, there were issues with drug manufacturing, which then Abbott left the scene and we don't have pro-urokinase. Other trials in the neurointervention era was ISAT. That was led in England and that led to the evolution of coiling of aneurysms as a standard of care. And this really set the framework for the development of neuroradiology.

But there was a gap of about -- of some years before there was, you know -- where there was new randomized trials of devices in stroke. And I think this is interesting. I think that it was an intersection between the academia and the way devices are regulated, particularly in the United States, and also the way devices are paid for, right, in the United States. And I won't -- you know, I mean, it's, I think, a tradeoff between how we pay for stuff, regulate stuff and innovation, which is required to get to where we are today versus doing randomized trials all the time. And I think, you know, Joe may be able to comment on this really well in relation to IMS-3.

But we went through and IME-3, Joe and the group took it forward with IMS-1, IMS-2, IMS-3, right, and we've talked about those results. And then, there were two device-related trials, you know, head-to-head device trials showing that device A was better than device B. I think in the academic world, we were never -- it was never proven, for example, that the MERCI catheter was the standard of care. So comparing the Solitaire retriever or the Trivascular stent retriever to the MERCI catheter, right, was important to show that those were better than the MERCI retriever. But it's not true to say at the time, the MERCI retriever was the standard

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of are, because it wasn't, right across the world, across the way.

So there was this intersection of, I think, this balance between what the academic community would tell you is the standard of care and what is required for approval and selling of a device. It's great to talk about the devices and how important they are. They are important. But without the team, without the speed of process, the evolution in imaging that happened at the same time and the uses of medical therapy as well, the devices are useless, right? So you can't -- you can't say that these things happened in a vacuum by any means. And I don't think that just because you had a great new device, because there's no doubt that the retrievable stents are amazing technology, but without the team and without the imaging, it wouldn't have occurred. So I think the evolution of the whole specialty has been extremely important, right, the team approach, the approach to imaging intervention and managing the patient in toto. A lot of things can happen well in the first 12 hours of a case. You can get everything better, only for the patient then to have an aspiration pneumonia, end up in ICU and have a terrible outcome because the next two weeks are spent recovering from pneumonia and they missed their window for significant rehab. So the whole team, the stroke unit, the stroke unit care and the rehab is critical to get this -- to get to the outcome that we want, right?

So these are the things that I think are true in our context. I mean, certainly when in Canada, we do look to the FDA for -- because -- and I think it's because of the market, right? So people come to the United States. This is the biggest medical market in the world. So therefore, the regulation of that market becomes really important. We are heavily influenced by that in Canada. I think one of the things that I've learned about the FDA is that it is different groups. So the drug group has slightly different operating characteristics than the

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biologics group and the device group. And that reflects the different things that they're trying to do. So there's context. And I also have appreciated more than there's evolution, that what we -- what is regulated now is different than what it was 10 years ago and different from what it was 20 years ago. And I would encourage everyone to think about the fact that we're existing in a historical timeline about how regulation occurs.

I'll skip through that. The other thing, I guess I said this about payment. This is another one that we talked about extensively at the STAIR meeting just past about whether we can use surrogate outcomes. And I think one of the -- it's great if we can. But we have never been able to show that they are fully one-to-one, you know, predictive of outcome. And that's going to always be our trouble. I suppose it's certainly fair to say in the case of devices that are meant to open up arteries, the outcome is opening the artery. That's the relevant sort of engineering outcome of the device. And then -- and then that might be considered important and we could make a connection with that. But we learned this, clearly that reperfusion is the issue. It's not just recanalization. And sometimes it's the time that it takes for reperfusion that's critical or the time that it takes until you can get to even a chance to reperfuse. And one of our problems in the past has been that we've taken too long to treat. So we did have these neutral trials. We've talked about those already. And then, we moved on to the recent ones which have all been pretty convincingly positive. And so, the consistency of effect is really important. So one of the key principles of epidemiology really is that if you have consistent trials in multiple domains, then that's a really important way for you to believe that this is actually true.

So key lessons that I think you learned from clinical trials in the past, we have to be fast. So neuroprotective trials enroll people late. Streptokinase trials enrolled people late.

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And these are the data from Geoff's modeling exercise using MR, that you have to be fast, 2 million neurons a minute. And so, minutes count in acute stroke. The second lesson is you have to image people, right? And I think it's fair to say that imaging is our biomarker. We are searching for blood and other biomarkers that will be helpful for us to understand stroke. But the degree of damage, the potential for salvage, the technical accessibility of thrombus. And we're gradually moving to a situation where we may be able to use an imaging-defined tissue window to decide who should be treated rather than a time window. There are people, of course, early in a time window who are not good for treatment and there are many people late in a time window who are good candidates for treatment. So we need to gradually move there. Specificity's important. I think stroke has to be speciated. It's a syndrome. There are multiple different types of stroke. It's not just as simple as ischemia versus hemorrhage. There's all the subtypes. In studies of hemorrhage, we've got to figure out, you know, what type of hemorrhage are we after. And then, I think in ischemia, right now we have the issue of what -- where's the arterial location. For example, one of our biggest problems in stroke is that 25 to 30 percent of our strokes are so-called lacunar in nature, from small vessel occlusions. We can't image them in real time. So we don't have a lot to know about how to treat them. A lot of it is empiric. We can't see the small vessels. We may be able to with 7tmr and that kind of thing as it comes down the pipe. But that's going to be -- right now, that's a big barrier to understanding what's going on in the acute phase. And the last thing is that I think trials are like this. They're the art of the practical. They need to be done quickly. And it's this balance between the right patient population, so that's the speciation of stroke, the right resources to get things done and the science of what you're trying to do. And as we talked a lot about in the last couple of days, the idea that in some situations, registries may be the answer, the way to

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answer a question rather than a trial. So trials are great. They do provide definitive proof if they're well-defined. But they're not the hammer to which every problem is a nail. Sometimes the best solution is actually to do a different kind of study. And I will stop there. Thank you very much.

[Applause.]

DR. KHATRI: Thank you. Thank you for inviting me to speak today. My name is Pooja Khatri, from University of Cincinnati. I'm a stroke neurologist. And I've been asked to talk to you about the future of stroke trials. Several of us in the room are actually coming off of the STAIR conference, which was a stroke, academic, industry and government participation roundtable discussion where we really talked for a day-and-a-half in great detail about the future of stroke trials. So I'm going to try to give you a very big picture overview in the next 10 minutes. We're running a little over on time and I'll try to be very succinct because I think the bulk of the wealth of this workshop is going to be the discussions in the rooms themselves.

So these are my financial disclosures. And I'm specifically going to focus on the future of acute stroke device trials, given that this is a device workshop and particularly from my academic perspective. I think it's helpful to think about what we know and don't know and where we're headed by putting things into a few categories. When I think about devices for recanalization strategies, I'm thinking about gaps in knowledge for patient selection and specifically those that are IV t-PA treated versus those that are IV t-PA-ineligible. And I'll talk a little more about that. But generally, the IV t-PA-eligible patients are going to be those that arrive later, those that arrive beyond the four-and-a-half-hour time window of IV t-PA. There will be a small subset that are IV t-PA-ineligible that arrive early. And I think that's a healthy dividing line as well. And then, there's always going to be room for improvement with our

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recanalization devices. And finally, there are going to be devices that are going to be used for neuroprotective strategies.

So focusing in on IV t-PA-treated patients and the endovascular device world worldwide, what I have here is kind of in the light red, which doesn't project very well. I apologize for that. But the light red would be ESCAPE, EXTEND IA, MR CLEAN, REVASCAT and SWIFT PRIME and THERAPY. These are all completed trials. Let me see if I can move this with the mouse. These are all completed trials, these trials in the light red, that have either been published or have had results presented. And they have largely enrolled IV t-PA-treated patients. The ESCAPE trial, run by Michael Hill, who just spoke with you, and others in Canada, among other countries, they planned for 500 patients and enrolled 315 and 238 were IV t-PA-treated. EXTEND IA had a halted early with 70 of 100 planned patients. MR CLEAN, 445 IV t-PA-treated of the 500 patients that were enrolled. And then, finally, REVASCAT with 150 IV t-PA-treated patients, SWIFT PRIME with 196 IV t-PA-treated patients and THERAPY, with 108 treated patients with t-PA.

So those are the ones that have been completed. And then, we have the ones that we are waiting for data on. There is PISTE, which has evolved into a new design. I won't get into the details in the interest of time. And THRACE, from France. Both of those also involve t-PA-treated patients and we'll be getting those results as they get patient follow-up. And then, finally, we actually still have two ongoing trials in this space of IV t-PA-treated patients. One is the BASICS trial. It's being run in the EU. They're planning on 200 patients and they have enrolled 66. The distinction of this trial compared to the ones that have been completed is they're including basilar artery strokes whereas the others were all anterior circulation strokes. It's a sicker population and I think there's been a lot of debate about

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whether we can randomize these patients, which is why they were excluded from previous trials. And now, we have to think about whether we can apply our previous trials to this patient population. And I'm sure we'll be discussing that in the breakout sessions as well.

The other ongoing trial, interestingly, is RESILIENT in Brazil. And I see one of the leaders of that trial here in the room. And that trial is happening in a very comparable population to those that were completed. But Brazil felt that they needed to do a trial specifically there because of specific intellectual and regulatory issues that they face.

So what I'm going to do is just kind of talk through with you what I think we know from the completed trial data that we have so far. And I think that we know at this point that we should open up arteries. But the question is whether -- not whether we should open up those arteries, but whose arteries to open and how. We had disparate design features in all of these trials. And I'm just going to hit on a few big picture ones to give you a sense of what we don't know and where we need to head. Each of the trials used different imaging selection criteria. You can see what I did was I sort of highlighted in blue here what was used. For example, irreversible ischemia, which could have been measured by aspects or core imaging with MRI, was used actually in all of the trials, probably MR CLEAN as well. They didn't specify. They had kind of a gray area principle for who you put in the trial. But certainly for all the other trials, there were explicit criteria.

The other trials, three out of five of them, also measured salvageable brain to varying degrees. I won't get into the details of that right now. And like I mentioned to you, MR CLEAN used the gray area principle. So one consideration here is do we know how best to select patients with imaging for endovascular therapy. The second consideration is do we know how mild we can go with acute ischemic strokes. The three of the five trials that have been

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published used an NIH stroke scale score of either 6 or 8 as the lower threshold. One used an NIH stroke scale score of 2. The other simply specified IV t-PA-treated patients. Among those that didn't have a lower -- or had a lower limit than that 6 to 8, there were exactly 14 patients with an NIH stroke scale score of 0 to 5 that were enrolled among these 1,200-plus patients. So another area where we've got a question that remains after these trials have been published.

The other one that we will struggle with is occlusion location. And we have basically a small minority of patients, 108 out of the 1,300-plus that were M2 occlusions, more distal than the ICAs and M1s. And again, we may learn some things from this dataset. But we probably have future stroke trials to sort this out needed. What about time to endovascular start; in other words, arterial puncture? Three of the five trials required that arterial puncture happen within six hours. The ESCAPE trial, led from Canada, had a 12-hour time window. But only 15 percent were enrolled in that 6 to 12-hour time window. And so, they weren't able to be conclusive about that group. And then, REVASCAT actually went out to eight hours. And you can see the actual median onsite to arterial puncture times there that range in the three to four-hour range.

We've had data building for a while in the field that time to reperfusion on average as it extends reduces the likelihood of a good outcome. And I'll show you here on the left the time to reperfusions in the recently completed trials. They were in the four to six-hour range. And I want to show you this graph that I found very helpful and kind of cool from Shawn Probcaram [ph] and colleagues, published in *JAMA*, where they plotted out the rate of good outcome from zero to a hundred percent and the average symptom onset to reperfusion time in trials. And really, you can just see that pattern really clearly, that the longer we go, the less likely we are to see good outcomes among our patients when we use endovascular therapy.

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So the question is how far can we push that. I think that there's generally patterns of data that are suggesting six to seven hours on average might be the most that we can push that. And we're really waiting for analyses from some of these completed trials to help us sort that out for sure. But it's interesting. As an academic, I just share that, you know, I've always found it interesting because the FDA clearances have been with the eight-hour threshold. And from my understanding, the rationale probably -- and this is not FDA input. This is just my own speculation -- is that it probably has to do with the fact that the PROACT-2 trial had a six-hour time window and a two-hour infusion. And so, there was a sense that you could kind of work out to eight hours potentially since the PROACT-2 trial, as Michael mentioned, was indeed positive, albeit with a borderline p value.

So where do we stand? I think it's actually the acute ischemic stroke guidelines update that was published by the American Heart and Stroke Association really kind of give us a nice framework for thinking about this. What we know with class one, level A evidence is that patients should receive endovascular therapy if they don't have baseline disability. And I'm not saying that they shouldn't receive it if they do have baseline disability. I'm saying this is who we know for sure we benefit when we do endovascular therapy because this is who was enrolled in these trials.

Treated with IV t-PA within four-and-a-half hours, with a causative occlusion being an ICA or M1, who are 18 and older -- no upper age limit here -- NIH stroke scale score 6 or more, aspect 6 or more, which is that measure of early ischemic change on a CAT scan, irreversible injury. So in other words, having relatively low to moderate levels of reversible injury at the time of treatment. And then, treatment initiated within six hours. So this is the population where I think that it's very unlikely we're ever going to do anything but an active

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comparator. And I think most people would agree in this room.

And then, I think where we get to the debate about issues, and this is where I think the future of our stroke trials are, are the patients that are treated beyond six hours. And that's where we need more trials. It's also debatable how to handle those that are within six hours that either don't have baseline disability, have uglier scans with more irreversible ischemia at the outset, have mild strokes and have the causative occlusions other than the ICAs and M1s, in other words, the M2s, the P1s, things like that. So this is another area where you can imagine that we have to sort out for the future how we're going to handle this population. It's hard to know if some of these are going to be trials versus some of these are going to be able to be answered by pooled analyses. And that's something I think everyone in the field is working hard to figure out.

There are pooled analyses planned right now. And I think that these will provide some illumination. As I mentioned, there's an academic VISTA-Endovascular collaboration. And there's been a proposal that I've participated in leading called TREAT, which has brought together the PIs of all the recently and previously completed trials to basically pool data and start to look at effect modifiers in this group as well as heterogeneity between trials and the statistical analysis planned is published. And then, I'm aware of industry-sponsored pooled analysis occurring as well. And so, these will hopefully give us some more information as we move forward.

So what about patients who were IV t-PA-ineligible? Well, that's where I think we really have the future of stroke trials. And no one knows that better in this room than Greg Albers, who was recently funded by the NIH to lead the trial that I've listed on the bottom here, DEFUSE-3. We just learned about this trial being funded in the last week or two. It's in the 6 to

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16-hour timeframe, NIH stroke scale scores of 6 or more. Here, we're using a more stringent imaging selection than just what I told you about irreversible ischemia. But we're actually looking for salvageable brain with perfusion imaging. It's going to use FDA-cleared devices with a sample size of 476. And everyone's working hard to get this trial started up.

And there are two other trials that are ongoing right now also addressing this space and moving along and hopefully will provide helpful and complimentary answers.

There's the DAWN trial that's sponsored by Stryker in the 6 to 24-hour range with NIH stroke scale scores of 10 or more. They are using a clinical imaging core mismatch criteria, which is a little more complex. And I won't go into the details again so we can kind of keep moving. But they're using the Trevo device, a 500-patient sample size. And they probably have updated numbers for me. But last I heard, they had at least seven patients enrolled.

AUDIENCE: Forty-nine.

DR. KHATRI: Forty-nine. Like that number better. I'm glad you shared that. And then, the POSITIVE trial is in the 8 to 12-hour time window, NIH stroke scale scores of 8 or more. And in this trial, they're allowing the local sites to define penumbra according to what they think should be the selection criteria. So there'll be actually some diversity there in who gets enrolled. They're allowing all FDA-cleared devices, 750 patients planned. Twenty-one enrolled is what I'd heard last. But is that where we're at? I see some nods. So that is indeed enrolling.

And so, that's for the patients that were beyond six hours. Within six hours, I will just throw out my personal opinion, which is I think that it's going to be really tough to do a randomized trial, even though we don't have great evidence. I think we as a field generally agree that when patients are within six hours, we need to open up their arteries based on some

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of the IV t-PA-treated cohorts that I told you about as well and the supportive evidence of some of those non- IV t-PA patients in those recently completed trials. So but that level of evidence is indeed C. So I'd just put that out there.

Devices have been improving over the years. This is a graph that shows you year of study publication from '98 to 2012 and rates of recanalization, keeping in mind that they're all defining recanalization a little bit differently, but generally all going in the right direction. So we're making progress as a field and the future of stroke trials does probably mean though doing even better at that because when you look at the data, we actually still have a lot of disabled patients even in these trials that showed us the success. I think these numbers are quite impressive. This is modified Rankin's 2 to 6, which means minimally, moderately, severely disabled or dead. In the MR CLEAN trial, 88 percent of patients would have met that. And it was still even in the best numbers, we're at almost half met that disability rate. And so, that's even with good and early recanalization with current devices.

So you can imagine that, like I said, we have to get more devices. And so, on the left, you've got the FDA-cleared devices that we have right now that many of you probably know, Penumbra, Aspiration -- MERCI retriever first, then Penumbra, Aspiration and then the Trevo and Solitaire stent retrievers. And then, on the right are some examples of what are in the pipeline, the Penumbra 3-D separator, the Neuravi, EmboTrap and the Medtronic LAZARUS Cover. The latter two are really targeted at trying to catch those embolizing clots as they're being retrieved.

And then, finally, I will just briefly end to say as much as we focus on recanalization, the future probably includes more than recanalization. And we may just be that even with the very best devices, we need to do more to just help out that brain tissue that's

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there. And so, some examples out there of devices that are coming out on the horizon with either current or planned trials include those that might augment collateral blood flow. On the left there, I have a picture of the BrainsGate device, which is used to electrically stimulate the sphenopalatine ganglion and thereby vasodilate cerebral vessels. And they have two trials going on, one in tPA-treated and one in non-tPA-treated. And then, on the right here, I have a picture of a device called the VitaFlow that is causing dilation of cerebral arteries by means of pulse magnetic stimulation of the facial nerves. And this is in very, very early stages of development.

There's also remote limb preconditioning, preconditioning meaning not setting off the ischemic cascade in a remote area before the incident ischemic event happened but doing it during the time that ischemic event happened. And so, the idea is someone comes in with an acute stroke. Well, at the same time, you do something like, you know, compress a lower limb and cause some transient ischemia with a tourniquet or a device and thereby set off various mediators that might help with cell survival that make it to the brain. And one ongoing trial is RESCUE BRAIN and I know of others that are in development.

And then, finally, endovascular hypothermia, an area that's had a lot of great data in the animal space. And we wonder if it's going to work in the human space eventually when we get our definitive trials going. The one that I'm most familiar with is ICTuS-2/3, which is led by Pat Lyden, who's probably here and is looking at using endovascular-guided catheter to cool patients during the acute ischemic stroke time period.

So I conclude that future trials need to address optimal patient selection for FDA-cleared devices. Newer devices to achieve recanalization more frequently and even more safely are anticipated and that our future strategies are probably going to include

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neuroprotection. And with that, I'll send you off so we can discuss this all in a lot more detail.

Thanks.

[Applause.]

**BREAKOUT SESSION INTRODUCTIONS**

DR. PEÑA: So I've been instructed by my staff to keep my comments very brief. So I think on you badges, you have numbers. And so, for groups, there's four groups that are meeting in separate rooms. Group 1A is meeting in the Pooks Hill Kensington Room. Group 1B is meeting in the Montgomery Democracy Room. Group 2A is in Salon E. And Group 2B is here in the Grand Ballroom. We'll be going immediately to start our breakout sessions. And I understand that folks, once you're in your rooms, the moderators will move. So you can actually stay in the room that you're in and we'll shuffle around our moderators for the sessions. Thank you.

(WHEREUPON, the foregoing adjourned to breakout sessions at 2:33 p.m., and reconvened at 5:11 p.m.)

**BREAKOUT SESSION SUMMARIES**

Dr. Pena: Hello? Okay. So I just want to thank everybody for attending this workshop. I think we've had a really productive meeting. I'm going to introduce two of my colleagues who's going to summarize some of the key discussions at the breakout sessions. So Dr. Dan Krainak will summarize the clinical study design and patient populations first. And then, Dr. Viveca Livezey will summarize the clinical outcomes and the safety endpoints discussions.

**CLINICAL STUDY DESIGN/PATIENT POPULATIONS**

DR. KRAINAK: All right. So I'll do my best. Anyone who participated can feel

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free to correct me. But it was a rapid summary, so. All right, so the first question we had was for acute ischemic stroke medical devices, what are appropriate control therapies. So a big summary is it depends kind of. So I'm just going to say that answer for everything. It's my favorite answer. So if it's within the cleared time window or if it's kind of within kind of current standard of care, that's one consideration. If it's outside of that, then the control is standard of care. So the control is usually standard of care. It's a bit fuzzy if you're combining different devices.

So some things are to consider were standard of care might depend on operator preference. You might have multiple devices. People like things that have control. If it has similar technological characteristics and safety profile, that was really important. There's a little discussion about what are advantages or disadvantages of what you picked the comparator to be. Should it be best available? And some advocacy for head-to-head comparison. And outside the cleared time window, then there's still equipoise. But it's pretty unanimous, at least in the groups I was in, that you cannot do anything less than the current standard of care. So whatever it is, you have to adapt to that. And then, there's a consensus on the goal is a high level of complete recanalization.

All right. Question two was what criteria or mechanism can be used to allow data borrowing among multiple studies or subgroups. Depends how similar the populations are. So inclusion/exclusion criteria are very important. When you have the same enrollment characteristics, that's an advantage if they're very different. There's a big kind of push for using it for hypothesis generating more than results. And there was some consideration that borrowing could be a disadvantage for smaller or newer companies if all the data's not publicly available, so a big push to make as much data as possible publicly available to level the playing

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field. Also just a note that FDA and payers and everyone else and other regulatory bodies use slightly different levels of evidence.

In the other group, there was a little more discussion about post-market studies and how you could use post-market data to build registry data and then potentially work from the literature. And that's also a call for high fidelity in registries. There's a lot of enthusiasm that might possibly be a venue for a subgroup analysis.

All right. Question three was what are the benefits and challenges of using consistent imaging assessments before and after treatment within the patient population in the same clinical trial and across all acute stroke clinical trials. Consistent imaging wasn't exactly present in the recent trials. And I guess I can represent the Division of Radiological Health and Imaging in trials that there's always a huge benefit to standardization within the context of clinical trials. And I think both groups skipped it a little because that had been talked about a lot at STAIR. So we look forward to those publications as well.

Let's see. Next question was in some cases some patients may require concurrent therapies, such as an acute ischemic stroke medical device in addition to carotid stenting. How should these multiple therapy patients be analyzed if the active treatment group is the acute ischemic stroke device? So there was a big push to prospectively define practice standardization. So before the trial starts, define what you're going to do. And then, I would personally add ensure that people do that.

So it's one thing to design a trial and another to make sure everyone follows the rules. It should be objective and streamlined across centers. There's definitely a stenting issue. There's potential confounds the outcomes and it needs to be accounted for in the study plan. And there was a little bit of discussion in the group I was in is, you know, how does FDA

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penalize a sponsor if, during the procedure, the interventionist moves to a different device.

And I guess the answer to that was prospectively standardize and define how you're going to account for that was the recommendation.

All right. Number five was in what situations in the development of an acute ischemic stroke medical device could a clinical trial not be necessary or should it be required for all ischemic stroke technologies, given that this is a high risk patient population. So could it not be required? Yes, was heard from the audience. And the kind of bounds on that were suggested that if a device is expected to have a similar effectiveness of the predicate, you should -- FDA should look at safety and there might be also potential opportunities for post-market studies in this arena. If the device is a really new paradigm, then those instances would need clinical data. And there might be a place to look at differences in age and IV t-PA. These might be able to provide answers without clinical trials. Sorry if I butchered some of that last one.

I had even less time to summarize the next answers. But I will try. Some were our best here. So this is about patient populations and selection. So for novel acute ischemic stroke treatment, is there a patient population that can be defined in which clinical equipoise still exists. If so, how can we define these different patients? And I have to put my answer -- sorry. So yes, in some situations, especially advanced time windows, larger strokes. Some said you can look at the AHA or SENS guidelines. There's plenty of areas with equipoise to expand to other treatment areas. I'm trying to see what else. This could be dependent on site a little bit. So not all sites may have clinical equipoise. And I'm trying to look. Low NIH stroke scale. Sorry. I was looking that in my notes and I've lost where I had my notes. So low NIH stroke scale. Small vessel, distal vessel.

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So all right. Number two, how can we design studies to select patients most suitable for a particular acute ischemic stroke medical devices. Kind of there's opportunity for generalizability. Some things to consider are locations, infarcts, volume. There was a big -- it depends on exactly what you're trying to study. So FDA asks a question. Audience says it depends. That's good. So most studies recruit proximal occlusions. So you could look at posterior occlusions, small vessels, et cetera. It depends on the endpoint a little. I heard a lot of anterior and posterior strokes are regarded as different. And smaller vessels need smaller devices. So it might have different -- more stringent outcome measures. I probably missed some stuff there. But I'm going to move on to the next question.

So what subpopulations of patients warrant examination in future mechanical neurothrombectomy studies to expand the safe and effective clinical use of these devices to a wider patient population. There's a lot of questions about better and cleaner imaging selection, especially for small volume infarcts. Small vessels, posterior occlusion outside existing time windows, a lot of the same stuff we mentioned before. Pediatrics were noted in particular as severely understudied. M2, M3 branch occlusions, stuff that's hard to reach by surgeons. Low NIH stroke scale. I know someone mentioned isolated aphasia.

So all right, number four -- sorry, I'm really running on the stretch of when we had time to summarize. But what key criteria can be used to allow combining patients across seemingly heterogeneous subgroups with different location size, etiology of the stroke within a study in order to make a broader device indication, that is to include acute ischemic strokes in vascular territories that may present less frequently than in others. I guess a lot of the same discussion above, kind of can we combine adults and pediatrics. It's really challenging to extrapolate. But you know, if you have pediatrics that are large in size, they look more similar

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to adults. You might be able to do that. And there was a lot of feedback that FDA is faced with a tough choice here because these studies are extremely difficult to run in these small patient populations. It's very challenging to get the data. So you have to extrapolate the data to similar populations and there were a lot of considerations.

All right. And I get to number -- so I didn't get to number five. But I'll say what number five was. How can you use enrichment strategies so that devices benefit the most appropriate patients? So -- if you want to -- no one got to that question.

AUDIENCE: [Off mic.]

DR. KRAINAK: Data sharing, data borrowing would be another opportunity here, probably similar registry information that you might look to. But didn't sound like any groups got to that. So now, I will turn it over.

**CLINICAL OUTCOMES/SAFETY ENDPOINTS**

DR. LIVEZEY: So I wish I could project it. But I'll try. Okay. So our groups dealt with -- let me see if I can project it, if possible. It's very messy. So please ignore that aspect of it.

DR. KRAINAK: You'll have to do some slides.

DR. LIVEZEY: Well, I was trying to quickly do them during your presentation. Okay. So we tried to deal with what are the key primary and secondary outcome measures that should be used routinely in clinical trials for acute ischemic stroke medical devices. So generally, we spoke about a lot of different ideas. In general, people thought the mRS really is the preferred primary outcome measure. We talked about whether we should use the ordinal versus the dichotomous or weighted mRS. And again, I think that it was felt from the academic standpoint, the ordinal mRS is what people are using and a shift analysis on that seems

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adequate. But the dichotomous and/or weighed mRS, they're still good probably as secondary outcome measures.

There was a lot of discussion about the NIH stroke scale, whether you should use a 24-hour time point, 48 hours, seven days. You know, there's been I guess some literature that has demonstrated that at seven days you can predict what the outcome is going to be long term if you look at the NIH stroke scale, the seven-day time point if you have an improvement of seven points on the NIH stroke scale. But I don't think there was a general consensus on what the best time is. So we're hoping that that's something you guys came help us figure out in the future.

We were talking about how these outcome measures need to be un-blinded. We talked about the PROMISE 10, but how it hasn't yet been validated in this patient population or in this patient. There was a little bit of discussion about enrolling subjects who, again, have a baseline elevated mRS score and how that might affect your data. And we also talked about -- oh yeah, how that might be something where we can move to in the future, enrolling subjects who have a baseline mRS that's higher.

Again, my font is changing here just to make it more exciting for you guys. So what is the role of patient-reported outcomes? And I kind of skipped over some of the other things because we kind of dealt with it within the first question. So it was very quiet in the room when we talked about PROs. And I don't think that's because people didn't think it was important. I think it's that we haven't really established what the important PROs are right now. Again, people spoke about the PROMISE initiative possibly being something to utilize in the future and that we might be able to use registries even to kind of gain data on which PROs are meaningful to patients and to their outcomes.

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So given our concerns for the translation of patient safety in the clinical trial setting to the real world, following premarket approval or clearance of acute ischemic stroke medical devices, how can registries be leveraged in the design of new acute ischemic stroke studies. So we talked about maybe using again the PROs, looking at the NIH stroke scale, the different time points, whether it's a 24-, 48- or 7-day time period, looking at imaging selection criteria. So Jim Grotta had a lot of ideas about how we could look at the previous data that's already been collected and kind of determine the sensitivity and specificity of the various imaging modalities and which were I guess the -- which might be identified from that to be more predictive of outcomes.

Oh, no. Okay. So I have seven minutes. Okay. So we also talked about looking at times, clinical outcomes, adverse events, 90-day outcomes, recanalization scores and looking at registry data to kind of look at safety signals that might emerge. They were talking about common data elements that you might enter. And we talked about this a little from the interventional radiology perspective, maybe looking at, you know, general anesthesia versus no anesthesia. How many passes were used? Did you use the balloon occlusion catheter or not? Was vasospasm present or not? And again, there's a lot of data to collect. So we couldn't come to a consensus on what needs to be collected. But you want to try to pick the elements that would lead to the highest yield.

So what procedures should be used to construct new registries? Some people suggested FDA should just mandate it, which I thought was interesting because we have required registries sometimes as part of our post-market clearance for devices. Sustainability was discussed, how these -- sometimes these registries come and go very quickly. So we need to pick one. We either need to use one that already exists or try to -- which I thought was --

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you know, some people suggested the SITS registry that's based out of Sweden or use the Get with the Guidelines registry and try to augment the ones that already exist.

And then, we also talked about how can we support the development of common definitions. Again, this was FDA should force us to do it. And then, we talked about again different common data elements that we should be looking at. And then, I kind of stopped with my PowerPoint because Dan stopped speaking. But I think the last question that was addressed or was asked was -- I think that's it.

Okay. We talked about using multiple societies to kind of come together to -- multiple societies, along with the government and industry to come together to create a registry. When we were talking about the next question was safety endpoints, what common risks can be applied to all acute ischemic stroke patients when designing safety endpoints for clinical studies. We discussed how whether you should use PH2 with or without neurological deterioration, subarachnoid hemorrhage, subdural hematomas, PH1, malignant edema, some other common risks were vessel dissection, vasospasm, new territory infarct and that these should be separated by the device, the procedure, unknown. There was a lot of discussion regarding how many passes should be used. And some -- and a lot of discussion as well about whether it's appropriate to use a four point or greater change on the NIH stroke scale because the NIH stroke scale could be affected by things like infection or pneumonia or comorbidities that can occur when patients are status post a stroke. A lot of people also referred to some publications that have come out lately that identify, you know, what adverse events occurred in these recent stroke trials.

Then we talked about even the kind of imaging you should use and whether sometimes when you do a CAT scan, you can see something that looks like contrast and you

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can't differentiate between hemorrhage or contrast. So they're talking about dual-beam CT being good or perhaps even requiring a repeat head CT if you're noticing what looks like contrast versus hemorrhage on a scan. We talked about the use of MRI possibly. And then, the second question for safety was we have previously required intracranial hemorrhage with a change in NIH stroke scale of greater than or equal to four points. Is that evidence of neurologic deterioration and are there any alternatives to this? People said, again, this is probably the best. But we need central adjudication for this. And again, talking about looking at symptomatic hemorrhage, not only PH2 and blinding assessors, especially when we're moving to device against device.

And then, what stopping rules? So I think the other group talked about technical failure to reach the clot in 30 minutes may be a stopping rule. And they call this the TFRC 30, which might be required if you reach that in more than 10 percent. Of course, in our group, we had a lot of different discussion about whether you should give a time limit to interventional radiologists when they're doing this procedure or not. We talked about embolism and new territory in both groups. But one group came up with a 15 percent and a symptomatic ICH of greater than 10 percent, one frank exaggeration or perforation or one death on the table. So these were some proposed stopping rules. We also talked about number of passes, whether you leave it to the judgment of the neuro interventionalist or not. And all these rules might be device-specific and protocol-specific. Some people just called it a plain, quote, "nightmare" trying to come up with stopping rules. Maybe to use the DSMV to help out with that.

So with the development of novel acute ischemic stroke medical devices in order to specify an appropriate patient population, the patients selected may have been treated with previous medical therapies. What are the increase disks to patients of multiple acute ischemic

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stroke medical therapies are used on the same patient and how can these been mitigated? So if you've received, you know, analytics or the new oral anticoagulants or aspirin or Plavix, you might want to look at bleeding. There was some discussion about do you stop intravenous alteplase, if you know, you're able to remove the clot during the procedure. But in general, there was some discussion as well about not only medical therapies but also device therapies that might take place during a study and why FDA does not allow certain devices to be used, you know, during studies and how we can kind of move forward with that. So those were the different topics discussed.

[Applause.]

**CLOSING REMARKS**

DR. PEÑA: So I have a couple of quick closing thoughts and comments, some recommendations that I think will be important to mention. But I also want to make sure that, you know, I do recognize folks. It takes more than one person. Some of the session moderators that were here, Michael Hill, Donald Frei, Michael Froehler, Pooja Khatri, Sameer Ansari, James Grotta, Patrick Lyden, Lee Jensen. Thank you very much for helping us moderate these sessions.

And I do especially want to mention the FDA staff. And please just be patient with me. But Hilda Sharon, Lin Jung, Lee Booth, Viveca Livezey, Jamie Waterhouse, Martin Ho, Laura Thompson, Murray Sheldon, Danica Marinac, Susan Monahan, Peggy Roney, Ja-An Lin, Dan Krainak, Gregg Kittlesen, Vesper Ramos, Michael Hoffman. This took a lot of staffing to do. And I think, you know, they should be commended. So I'd like to give the folks a round of applause.

[Applause.]

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DR. PEÑA: So we had a number of note-takers in each session. I know you heard a very brief summary. But we will be very carefully looking at the notes that were taken. I think we had at least two staff members in each session because, you know, it's nice to achieve consensus on stuff. But I think sometimes also where the real challenge is, is when you're trying to address each of the individual issues that were raised. We certainly appreciate the time that you invested in this workshop.

This workshop is part of an approach where we hold a public meeting as part of good guidance practices to get the input from stakeholders to further develop our guidance. It's not a great practice if we develop guidance without input. So this actually follows along good guidance practices, which FDA needs to develop, update guidance for devices we regulate. And now that we have a registration list and -- and I can't promise, but I will do my best effort to make sure that if there are updates in this area, we will try to let folks know now that we have your email addresses and registration information. I would encourage you though just to keep up to date with the website. We might have different updates on neuro devices as appropriate.

The second comment I wanted to make was, you know, the best way to -- the best way to get a device to market is to come talk to us early. And we have a pre-submission process for this. A lot of folks I see in the audience have used this process. Usually you can get a response within 90 days. I know folks -- there's been some issues where we've had some challenging applications, which have taken a little bit longer. But that's really the best way to proceed forward because then we can give you the front-end advice. And it's much easier to work with you on that side rather than trying to adjust for results when we haven't had a chance to work with you on the clinical study. So that's a second point.

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And last, thank you. I think this workshop provides a little bit more transparency to FDA. It's not a magic place. It's folks that have expertise that I think we are committed to getting products to market. And I think we appreciate your dedication and working together on this. So, safe travels and have a great evening. Thank you.

[Applause.]

(WHEREUPON, the public meeting concluded at 5:36 p.m.)

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CERTIFICATE OF NOTARY PUBLIC

I, ERICK McNAIR, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was recorded by me and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

*Erick McNair*

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ERICK McNAIR  
Notary Public in and for the  
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I, BENJAMIN GRAHAM, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

10/16/2015

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