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Please stand by. Today's conference will begin momentarily.

Good afternoon. Thank you all for holding. Saddam placed in a listen only mode into the question-and-answer portion of today's conference. I would like to remind all parties that the caller stamping recorded. If you have any objections please disconnect at this time. I would know to turn the call over to Andrea Furia Helms. Think you may begin.

Thank you. One moment. Good afternoon everyone. Thank you for joining us for today's talk on designing and performing clinical trials, and overview. If you have any technical questions or experience any technical difficulties during the webinar, please e-mail Dan, using the e-mail address at the bottom of corner of your screen. As always we ask you to take note of any questions you have for the presenter and ultimately the and of the presentation. At the conclusion of the presentation, the operator will take them in the order they were received. You will have to press\*one to get into the Kubrick

At the reminder we're going to record the session so that it will be available for those who are not able to join or if you would like to hear the presentation again. If you are not comfortable being recorded you may logout and disconnect now and listen to the presentation at a later time.

Today I had the pleasure of introducing Dr. Anne Zajicek. Dr. [ Indiscernible ] is a board-certified pediatrician and pediatric clinical pharmacologist who currently serves as chief of the abstract trick and pediatric pharmacology and view to predict ranch at the [ Indiscernible ] Kennedy Shriver national Institute of Child health and human development. She received a bachelor's degree in pharmacy from decaying University and a Pharm.D. from the State University of New York at Buffalo. She completed a postdoctoral fellowship in the Department of pharmaceutical test pharmaceutics at Saint. Jude children's research Hospital. Anne service and assistant professor at the University of Colorado so cool of pharmacy and a clinical pharmacist at national Jewish Hospital and research center. In 1991 Dr. Zajicek entered medical school at the University of Pittsburgh and in 19 gosh 1998 computer the residency in pediatrics at the Children's Hospital of Pittsburgh. She practice primary care pediatrics for two years and then continued her training as a pediatric clinical pharmacology fellow at the Stanford University. She subsequently joined the US FDA in the office of clinical pharmacology and maillot pharmaceutics and she joined and I CHD at the pediatric medical officer in August maillot pharmaceutics and she joined and I CHD at the pediatric medical officer in August 2003. She was appointed chief of the abstract. And pediatric pharmacology and therapeutics branch in 2010. The branch is responsible for the NIH implementation of the best pharmaceuticals for children's act and manages a portfolio of basic translational and clinical research and training grants in obstetric and pediatric pharmacology. Auctor Zajicek, turn it over cheaper things for joining us today.

Thank you very much. Like to be here. I will talk, I have a 38 slides. I hope you can hear me. Then at the end of that, feel free to ask questions. There have been many books on the subject so I am truncating this down to I think 38 bullet points here of what is think is important but again feel free to ask questions when I am done.

I wanted to talk first of all about what exactly a clinical trial is and I think this article in the New York Times from a couple of weeks ago does a really nice job of explaining what that is. This quote is when you do any kind of trial you're really trying to answer a question about choosing the universe. Of course we cannot know that so we try to design an experiment on subpopulation of the world that we think is generalizable to the overall universe, that is to patients who would use the drug. The subtext of this is two words that I will be talking about including the sample and the population. We do have clinical trial or some sort of experiment on a smaller subgroup of the entire world's population called the sample but we are hoping that those results would be generalizable to the general population, people who will be receiving the drug.

To read to illustrate the point that why clinical trials are important this is a slide from the Journal of critical oncology from May 2012 showing the overall survival of children enrolled in clinical trials in the children's oncology group. You can see the survival improvement from 1990 through 95 two 2000. One of the key points here is that the children's oncology group [ Indiscernible ] section between clinical trials that adult clinical trials is there is relatively any it is introduced into the oncology population for children. However, because of the very careful clinical trials that the children's oncology group has performed this survival has gone up considerably so this is a nice, again illustration of the utility of clinical trial.

There are many types of clinical trials. These are a few from, apart from a Wikipedia, prevention trials, screening trials, diagnostic trials, treatment trials, quality-of-life trials, compassionate use trials which is sort of a subtext of the treatment trials and I will be focusing on the concept of the treatment trials. There is a test for experimental new treatments, new combinations of drugs or new approaches to surgery or radiation therapy and again we will talking at this context about that drug.

There are generally three phases of a clinical trial but I added the zero and the for just for completeness. Phase 1 is a dose ranging safety study generally normal volunteers unless it is an oncology trial in which case it would he tested in oncology patients. Phase 2 is a preliminary efficacy and safety study this time in patients. These are people with the disease of interest. Pastries if pivotal trial to provide cash to prove efficacy and safety practices for the purpose of life as labeling. There is someone call the phases are the micro-dosing trial. To get an idea of the drug pharmacokinetics in other words we take the drug orally or intravenously what have you, the drug concentrations have a time course with a concentrations are very low and a peak and go down and that kind of information in humans is important to determine the [ Indiscernible ] and the dose for the [ Indiscernible ] cash for the study. Phase 4 is the postmarketing safety surveillance study. During the trial it is possible to determine efficacy. It is difficult to determine the true incidence of a safety problem in a smaller or sample population. After the drug is approved, the FDA frequently asks for a postmarketing or phase for a safety surveillance study were now the drug use is being expanded from the sample population into the population.

There are several terms associated with clinical trial designs. These are a few of them. The standard is that drug trial would be done as double-blind, controlled, placebo-controlled, randomized I just wanted to explain these terms. The Brenda -- block randomization is not all that obvious. Your the treatment arm is determined by chance and here I describe a couple of ways at looking at the this where a would-be treatment ANB would be treatment be so the first person enrolled in the trial would be randomized to treatment a and the second page of the to treatment be and so on and so on.

However, typically the randomization Darla the more complex than that. It could be that the first two patients are randomized to treatment a in the second two are to treatment be or could be more complex like the third one. There could be a randomization of a one-to-one randomization, a 2 to 1 randomization where in the 121 case you would have the standard therapies arm one and the new treatment is arm into and then you would have one patient arm one and an equal number in each arm. You could expand that to have to patients in the treatment arm versus one in the standard arm and so on. There are many ways at looking at the randomization.

There is also block randomization where randomization can be for treatment as well as by age. This is especially important in pediatrics or by the site, the clinical trial where they are frequently obviously more than one site for a clinical trial.

There mostly generally speaking controlled, can -- controlled to mean a lot of things including placebo-controlled we will get to that in a minute where the compared arm is a placebo. Controlled meet test meaning there is inherent to protocol that it is not sort of a random post top data. There is recording of all efficacy and safety data.

As far as blinding goes, if the trial is unblinded it means that the patient knows what he or she is receiving and the investigator knows what he or she is receiving. Single-blind be that the patient is blinded or not aware of what he or she is receiving. Double-blind means that the patient is unblinded as well as the investigator.

The comparator arm could be basically two things. Either an approved a product for the same indication or the standard of care for given click condition or could be a placebo which should be completely blinded as sodas not possible to determine which is the active product in which is the in active product which would be the placebo.

[ NULL ] Brooktrout does not necessarily mean that patients receive no treatment . Frequently there could be a placebo plus the comparator, the active comparator versus the new agent plus the active comparator. It does not necessarily mean that the patient is not getting any treatments. For conditions where there is no accepted treatments, frequently the placebo is requested and it is especially important to test especially for behavioral and health conditions with the high placebo effect. We are frequently for example antidepressant medication several trials are required to get even one positive trial.

Study endpoints can include endpoints such as biomarkers. There is active discussion right now about the use of the dystrophin as a biomarker is a test for efficacy, the drug use for Duchenne muscular dystrophy. It could be surrogates where essentially the measurement such as the blood pressure measurement or cholesterol measurement are considered to be equivalent to the conditions of stroke for example. There are some nice FDA publications about how to go about validating various biomarkers for surrogate.

For endpoint validation, this does get tricky for some indications. Frequently therefore clinically relevant endpoints such as death, event free survival in the case of oncology products, overall survival. They can be clinically accepted, there is a validation process and again it would be very important before beginning a clinical trial to discuss these endpoints with FDA to make sure that everyone is agreeable with them.

This is an example where a biomarker didn't quite work out the way they thought it would. This is a famous trial that was closed in 1989 for safety reasons. This is report by the New England Journal. A preliminary report defective of and denied in flex tonight on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. This is a trial, the cardiac -- the cast trial which was set up in 1980s. Their point was to see if three different drugs would suppress ventricular premature depolarizations in people who have had a myocardial infarction. They decided to include a placebo arm and what they found was that this incidence of premature ventricular depolarization was actually not a good biomarker because during an average of 10 months of follow-up, the patients treated with the active drug had a higher rate of death from arrhythmia than the patient's that were assigned a placebo. This case it was better to be in the placebo arm than the drug arm.

This next slide shows the Kaplan Meier survival curve here. What you can see is that the upper darker bar is actually the placebo arm and that lower stairstep shows the declining survival in the people that were randomized a drug. Again, the trial was stopped early for safety reasons.

There are many ways to design a clinical trial and one that is having some discussion right now is called the adaptive clinicals trial design. According to the FDA's website and I have included the URL there, this is a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design or hypotheses based on an analysis of data, usually interim data from subjects in the study. What this means in English is that when you design a trial comes you have something called stopping rules or some sort of interim analysis which will allow you to make some assessment on how well the study is going or whether it should be basically redesigned in the middle.

This is an adaptive study design. It was another nice commentary which actually followed over the second slide about the failure of clinical trials talking about a child that is going on right now called the I-SPY2 trial. The end of the trial is sponsored by the biomarkers Consortium a partnership that includes the foundation for the National Institutes of Health, the FDA and others is to figure out whether neoadjuvant therapy for breast cancer, administering drugs before a tumor surgically removed, reduces recurrence of the disease and if so which drugs work best. As with the Herceptin model, patients are being matched with experimental medicines that are designed to target a particular molecular subtype of breast cancer. At the mike in other trials -- investors included Dr. Barry aren't testing up to a dozen drugs for multiple companies using up those that don't appear to be working and stubbing in others without stopping the study.

This is an example of an adaptive style test trial design which we do interim analysis but splendid the beginning of the study with bopper protocol and that if patients are doing well, or not doing well the patient to are doing well continue on their medications and he wants it or not doing well are started on a new medication.

There are various ways of powering a study and we're going to get sued -- to some of the statistics here in a minute by two general types of critical trials include a superiority design or a noninferiority design. In the superiority, the goal is to determine which arm is better. Is one are better than the comparator. Distance to need less study subjects. For noninferiority, which are determining is that one arm is not worse than the comparator and this tends to need more patients.

Power is a frequent issue in clinical trials. What is called the type I error, you have probably heard this in conversation is the ability to detect and accepted there isn't one, so in other words a false positive, type I error and the probability of making this type I error is called alpha. If you do not detect an effective there is one or a false negative that is considered a tribe to error and the probability of making a type to air is called a tab. There are equations of statisticians use in order to determine the number of patients needed for a clinical trial using a set amount of alpha and beta.

If there are too few patients enrolled in a clinical trial this is called an underpowered to trial. This leads to problems with statistical significance of how to interpret the findings together problem is that frequently in a clinical trial you wind up with incidental findings like you randomized 100 patients and a five in one arm seem to have some side effect or some beneficial effect that is incidental and this gets complicated in interpreting the clinical trial results because you're not sure whether this is a real findings board is an accident because there were so few numbers of patients.

The statistician as a mentioned is integral in key designing a clinical trial. The statistician determines that the study power and performs the interim analysis.

How many quick clinical trial patients do need for a clinical trial? This is an ongoing question because obviously it is easier for the sponsor to do a smaller trial as opposed to a bigger one and we get back to this attention between the sample and the population. If it is a very common indication then it may mean that your sample size will have to be fairly large. In the case of where disease is sometimes your sample is in fact the entire population of patients with the disease. More patients equal higher trial cost but it definitely equals better statistical powers you can feel comfortable with the results you saw in the phase 2 or the phase 3 study will be applicable to the phase for population or the population as a whole.

Trials can be stopped, should be stopped for multiple reasons. Generally again and interim analysis or an analysis of the trial at some point in the middle of these trial is planned. There are various stopping rules including stopping for food -- futility. In other words if you have gone to let's say half the trial and it looks like no matter how many patients respond or do not respond both arms are the same and there is no point continuing. The trial will be stopped for futility. This is a real ethical issue because you do not want to have patience intrigue into a clever test critical trailing of the trial will be stopped or you know for sure that one arm works better than the other or one arm is less safe than the other. This is -- the stopping [ Indiscernible ] are built and almost all clinical trials impacted think all pretty study can also be stopped for efficacy if it is clear that one arm is better than the other and it is unethical to enroll patients in an armor you know one side is not going to work as well as the other, the trial would be stopped. The same thing for safety as we saw in the CAST study that clearly there was a safety single, the placebo is significantly safer than the drug and the trial was stopped.

This is an interesting issue is clinical trials in terms of the timeliness of the trial. At times there are changes in practice and the trial needs to be, can only be done now and not later because later on the one arm will become a standard of care. This happened during the, there was a trial of interfering versus 10 84 chronological leukemia. [ Indiscernible ] a lot of side effects and that may have left so it became a time crunch to get that study completed. We had an experience which I will talk about at the end of this. The clinical trial the anticonvulsants were compared against [ Indiscernible ] for children with seizures that were not stopping, status epilepticus. However in the middle of the trial emergency transfer personnel started administering anticonvulsant entrance port so this affected the clinical trial that we were performing.

I wanted to move now to some specifics about clinical trials in terms of design and performance. For design the question is what is your specific question? It is got to be extremely specific otherwise you will not get an answer out of the trial. UD to determine what your efficacy and safety endpoints are. Is your endpoint or outcome measure validated and is it a griddle with the FDA? The other question is can this study be done? Is it feasible? Is it affordable? We will get to these bullets in a second. The other question about the performances who will manage the trial? Are there enough accessible patients who will meet in Rome at criteria? I'm a pharmacist of this was is special interest to me, do have a dosage form that your patients can take? This is particularly a problem with children.

This is a little off-topic here but just in terms of when you should meet with the FDA in developing a new drug, there is typically meeting with FDA before the submission of the investigational new drug application. This is discussed -- to discuss her plea cocoa work including preclinical toxicology including reproductive toxicology. The FDA typically would like to see three models preclinical models, to rodent and one nonroad but again it depends on the therapeutic area. Would like to see the efficacy in your free clinical model and an estimate of the first in man dose and dose escalation plans. At the end of phase 2, typically again another meeting with the FDA to discuss the results so far and the plans for the phase 3 trial again including safety efficacy and dosing endpoints.

I'll dimension these again but the FDA practice guidelines require that a clinical trial we use good manufacturing practice, good laboratory practice and good clinical practice.

The reasons for failure of clinical trials, the list goes on. Some cases the preclinical or animal model did not correlate with the human outcome including efficacy and safety. This is a frequent problem. As a safe you can cure cancer in mice that would have been cured about 40 years ago the results don't necessarily correlate with the human condition. The wrong dose was used. They were in a series of papers talking about some studies, the antihypertensives and children were probably the wrong dose was used and that was why there was a lack of effect.

You may be unable to recruit eligible patients. You may not have relationships with those sites in order to recruit them. They may be difficult to recruit. There is sometimes patient dropout in the middle of a trial or you needed 30 days of follow-up or two years of follow-up and you simply lost track of the patient's.

It could be that the biomarkers are not validated such as that CAST trial or are not correlated with outcomes . This came up with the [ Indiscernible ] a couple of years ago where a vast and decrease the size of the tumors but the mortality of the [ Indiscernible ] arm was not better than the control arm. It could be that you are you using on validated outcome measures and this is frequently a problem with Haverhill problems with -- or maybe failure to adhere to a good manufacturing actresses, good laboratory practices or good clinical practices and in particular failure to get informed consent from parents or legally authorized representatives. It could be that there is a discrepancy between the smaller phase 2 study and the results of the larger phase 3 study.

I next wanted to move to the clinical trial elements on other words basically who is involved with these clinical trials, who are they, what are their relationships and so on. At the top of this is the FDA, the FDA also the European medicine agency. Most pharmaceutical companies have a vested interest in having drugs approved by the EMA as well.

The sponsor is the entity which is paying for the clinical trial. In my job under the best pharmaceuticals for children Zach my branch is performing several pediatric clinical trials and so we are for the purposes of FDA labeling so we are functioning as a sponsor but more frequently is generally the pharmaceutical industry.

Under sponsor I have the data monitoring committee and the data coordinating center and I will talk about those in a second. There was a contracting person in the case of the government comes a contracting office which develops the contracting relationship between a sponsor and the principal investigator. The principal investigator works with the nurse coordinator who is responsible a lot of times for doing the action patient recruiting. There were recruiting sites and in the recruiting sites would be again another principal investigator there, and other nurse acquitted of the institution review board investigational pharmacy, patients and parents.

There are several other points I missing here but this is I think the most important one. In terms of the clinical trial Who's Who. We have the sponsor, pays for the trial, develops the protocol, is ultimately responsible for the study conduct. He principal investigator is responsible for performance of the trial as written in the protocol. The data coordinating center is usually a contract research organization or CRO which is responsible for monitoring sites, tracking enrollments, for drug accountability at the site and also is responsible for performing regulatory activities such as sponsoring regulatory paperwork such as investigation on new drug applications through the FDA and possibly the EMA.

For trial management, for contracting, this get slightly complicated about how to organize payment to the investigators and for patient enrollment as well as the investigator time. The data trial management is also contracted to test and query resolution. The tracking, under the contracts for the sites these are specified in the site contract. The important thing about this is that when the sponsor makes the relationship, confirms the relationship bike contract to the site there are certain recruitment goals in other words if the site is not having -- is not capable of doing improvement the site will be replaced.

The data monitoring committee is a vital to all of these clinical trials. The data monitoring committee also monitors the safety monitoring board is a group of external advisors who are unconflicted so in other words they are not involved with the clinical trial, they're not being paid by the clinical trial, they're completely separate and non-conflicted. The members of the DNC's typically include a chair of the data monitoring committee, a statistician, and ethicist, a patient representative, again the ethicist of the patient representative are very important in these committees in order to assure that the study is being done under good ethical practices and that the patient representative frequently gives real depth to the DMZ in terms of the effect of the trial on the patient population for example.

Then also the medical specialist. The medical specialist in the case of the status [ Indiscernible ] traveled be a pediatric neurologist of these are the people who make up the data monitoring committee and frequently there are other members as well.

For the clinical trial Who's Who, we have the contracting officer who facilitates the contract between the sponsors and the sites. The site principal investigator who oversees study activities that his or her sites. Because this person is also potentially conflicted it is important that this person also should not be recruiting patients. We want to make clear is that there is a study questioner, a scientific question the patients are being recruited to use the trial should not be feeling that they are under the gun so to speak to sign a consent form.

Dinners a coordinator oversees study recruitment, completion of the paperwork of the study including the case report forms, data entry and works with the CRO, the contract research organization to schedule monitoring. Researcher pharmacy controls the study drug supply, the dispensing antidrug disposal. In some cases may be responsible for randomization of the study since the pharmacist is typically not seen the patient. And would be bonded or could be unblinded.

Other people involved with the trial includes laboratory staff if there are blood draws involve further kinds of tissue samples. Pharmacologist including those that designed the study, selected dose and determine the concentration effect relationships which would inform the decision about the dose.

I wanted to talk briefly about a real-life example of what happened during our clinical trial comparing lorazepam and diazepam for status epilepticus. The background is that we had received a written request, letter from FDA asking us to perform this clinical trial comparing lorazepam against a diazepam. The question was that diazepam had been labeled for adults and questionably for children for status epilepticus. However lorazepam is really more the standard of care although was not labeled.

The question in terms of designing the clinical trial was, is to raise up am better than diazepam in treating status epilepticus in children? The question here, we're talking superiority trial. If lorazepam that are then diazepam works the secondary question is, is lorazepam is safer than diazepam wax then --? That we get to the next about those words may and is there a difference in efficacy or safety in children of different ages?

To drill down to what exactly we are talking about, that are and safer. In terms of the better, how are we defining status epilepticus? This was a question that came up, how long does the seizure have to go on in order to be considered not just an epileptic seizure but actually status epilepticus in other words the stat -- seizures not going away on its own. Another question was, seizure recurrence pics free: people have seizures, in this case children they might have another one in another hour or two so the question was was one drug working longer than the other drug in terms of seizure recurrence. The other question had to do with safer. One of the clinical endpoints of that occurs during these kinds of trials I'm especially for drugs that are used to treat seizures is that sometimes people have problems of breezing any to be incubated so one of the questions was is one drug -- our children being randomized to one arm needing to be incubated more than the other arm.

A question that comes up when you are designing a trust how many people have the disease of interest? Me in this case, no children in the US are seen in the emergency room in status epilepticus? There a couple of different ways of getting at these numbers. One is called the ICD-9 code comes international classification of diseases billing code. One important point is that these are billing codes as of these are not codes of that were designed to diagnose something. These are designed to build an insurance company. There is sometimes a discrepancy between Haitians being described as having an ICD-9 code for a certain condition and the number of patients who have that condition. There also insurance databases which have databases of the numbers of additions and numbers of drugs however one of the problems there is that those are databases are typically not linked as a you can get an idea of how many children might have been billed to have status epilepticus or how many children received diazepam or lorazepam but is hard to connect the two.

The other question which is a little more granular is in the sites that you are planning on contracting with the for this study, how many patients did they see in the last year? In the last two years that have status epilepticus number be a better way at getting at the the ICD-9 codes.

For study endpoints, we needed to have a consensus on the endpoints included the efficacy endpoints. Again going back to the previous slide, the definition of the condition come the definition of status epilepticus, the timing of intervention, did it have to be done in the first 5 min., 10 min., as fast as you can get an IBM? When should -- IVN. How long should be following the patience for recurrence of status epilepticus? For the safety points, incubation, awesome hospitalization and for all critical trials hospitalization and death would be considered serious adverse events and those kinds of adverse events would he recorded.

Then we come to the issue of feasibility. Can the study be done? One question that came up or do much right away had the issue of consent. It is critical actually mandatory of course that you get consent from either the patient or the patient's illegally authorized representative, parent, what have you. This is an extremely difficult problem in emergency situations where you cannot appropriately explain to somebody about getting informed consent in an emergency situation. After about two years of discussion with the FDA we were issued in exception from informed consent where there was a way for in emergency situations that included very specific regulatory guidelines about informing the community, pre-consent and so on.

The second question was the number of eligible subjects. The issue of pre-consent came up with FDA. We did attempt to pre-consent children who were likely to come to the emergency room with status epilepticus that there were very few children eligible. The other question came up about eligibility was for the purpose of this study, patients who had received benzodiazepines, in other words lorazepam, diazepam in transport before arrival to the emergency room were ineligible. This created a problem because this became standard care in the middle of the trust of ended up extended the number of clinical trial sites.

One ongoing question when designing the clinical trial is are the inclusion/exclusion criteria are too restrictive? Here is an example. If you wanted to test a drug that would reduce body temperature in the case [ Indiscernible ] patients but you wanted to exclude everyone who had received Tylenol for example, acetaminophen or ibuprofen, you might have a problem because it is likely that those patients with fever probably have received an anti-[ Indiscernible ] already and sometimes clinical trials do fell for this reason, the inclusion/exclusion criteria are too strict and you end up taking out enormous numbers of patients who would otherwise be eligible.

In terms of the status epilepticus trial, again our consent process, we did receive exception from informed consent from the FDA and their are several processes within the exception form informed consent including community consultation procedure where the sites that we were going to be working with were responsible for putting together a process to discuss with the community. In other words the geographic committee or the community of parents with the children with seizures to discuss with them what was going to go on during the clinical trial. We also had extensive conversations with the institutional review board to familiarize them with this process which had never been done before in children.

We also would issues about the EMT administered anticonvulsants will be needed to expand the number of sites that we had. Some sites were not able to recruit and we had to increase the number of trial sites.

In summary, clinical trials are quite complex. They involve many people. They tend to be quite expensive. They must be extremely well-planned and executed. They must be performed in compliance with FDA guidance and as I mentioned before the trial design, the endpoints should be discussed with the FDA as early as possible in the process that you are getting off on the right foot.

That concludes my talk.

Thank you Dr. Zajicek. Operator we will start taking questions now.

Thank you. At this time if you'd like to ask a question please press\*one on your touchtone phone and you'll be prompted to record your name. Please and mature phone and the clergy name when prompted.

All?

Good morning thank you for a much, good morning out here in California. Thank you very much. An interesting presentation. Basic building blocks for errands for children that are not used to trials. My question this morning, the patient population I am involved in is a rare diseases [ Indiscernible ] one and 1000 probability of having the genetic disorder which means we only have six or 7000 patients in the US. Trial size versus patient population in the statistical evaluation for a well powered trial, if we're talking cancer or something that happens much more frequently you have relatively huge populations to choose from relatively. Compared with something like [ Indiscernible ]. How do you get a well powered trial with such limited numbers of patients?

FDA has really been working on this question. I do seem to have been quite flexible in these areas of rare diseases for this exact reason that they simply aren't 10,000 patients to hypertension on. I don't have any conditions off the top of my head. And of this discussion about [ Indiscernible ] must Gillard dystrophies in the same kind of population whether having discussions about biomarkers. This is information that has been in the public press am not sure anything that is confidential. Talking about dystrophin as a biomarker for Duchenne muscular dystrophy progress think the point there would be question number one are the natural history studies, of these rare diseases so know when you have an intervention that something has happened.

Also, if you have some sort of firm endpoint, whatever that is. Have you determined, do have natural history studies in this population?

Yes we've done a good job with an organization called [ Indiscernible ] research alliance is powering a study covering eight or 10 clinical sites around the country. That has been going on for like 10 years. The problem is that the symptomology is not very crisp. Loss of balance, ability Dashti small finger dexterity -- small finger dexterity. It is not very accurate if you will.

Understood. I guess this would be a conversation to have with FDA. This has come up with the pediatric conditions like with the [ Indiscernible ] test. You always have to be old enough to do that and through the same thing with the 6 min. walk test you have to be walking in the first place. This does become an issue. I would have some thorough conversations with the FDA review division about exactly what they would consider a validated biomarker or clinical endpoints were you could actually see improvements but again that test would have to be agreed upon with the FT -- FDA review David -- division.

Thank you.

Jim?

Thank you for an excellent presentation. You made a comment about clinical trials being very expensive. At one of the FDA hearings the sponsors were talking about having spent $800 million to conduct the clinical trial. On the other hand the public is up in arms because of the high cost of the new drugs and treatments. Is FDA doing anything to help the sponsors, the industry to reduce the cost so that maybe the cost of the drugs won't be as high to us consumers?

I do not work for FDA so cannot speak for them but my personal opinion, nongovernmental opinion is I think these new trial designs I think will be helpful. For example, that trial with breast cancer, to set up a trial and then to close a trial in open a new trial again would be just horrific where as if you could do some sort of other alternative trial design cannot stop the trial in the middle but start the next treatment after the first one fails, these are attempts to decrease in the numbers of patients enrolled. That is the point, to get to an answer sooner. In that regard, these other types of clinical trial designs I think are one attempt.

I know the small biotech submitter trying to get some drugs or treatment approved just don't have the financial resources to be able to do the kind of clinical trial that is required. It really gets difficult to get these new ideas sampled and try to CVB, useful for us.

Yes, this probably went involve the biotech's but looking at the observational trials, databases and, that kind of thing I think can in some way be helpful. Again this would be more helpful for drugs that are already on the market but in terms of looking at large numbers of the population not samples anymore that have received drug, what is the safety signal that kind of thing, I think again those other kinds of clinical trials designs I think the goal is to try to [ Indiscernible ] some of these enormous dome old blinded trials and try to bring the patient numbers down and again find an answer sooner rather than later.

Thank you.

Mortimer.

Good afternoon, thank you again for sharing your intelligence was SM bring it to us a lot of information that we otherwise would find it hard to get. May I direct your attention to join me in the slide number 12 the. I have a question about that. It is called slide number 12 the comparison by percentage of placebo or the active treatment drug regarding days after randomization of survival.

Is called figure 1, survival among 1455 patients randomly assigned to receive the drug or the other drug or the placebo.

Is the epoch cat trial.

The trial was ended at the 500th day after randomization. I am looking at the data in this graph and it looks to me that even after the first 100 days there was a pretty clear differentiation between the survival percentages of the placebo patients and the others. After 200 days, was even more marked and so on. Why did they wait until 500 days when the indications were apparent so much earlier we expect that is an interesting question I want to have to go back and read the New England Journal paper but as I was reading it to me there were two studies embedded together. Study one was the study where they were actually looking at dose ranging.

The purpose of this trial was the phase 2 a where they were during the dose ranging and then the bigger study was supposed to be a large efficacy trial. They were not expecting this so I don't believe, could be wrong because I have not read the study in a bit but I don't think we were stopping rules embedded in their. This was the natural and of this part of the study where they are looking at dose ranging.

If they had known in advance always the number one they wouldn't have done the study because they were completely off-base with looking at the PDC but this was obviously completely unexpected but this was the natural end of this part of the study.

So if there are no stopping rules, nobody pays attention to just buy normal intelligence and looking at the material? Nemec know, typically even --

To believe that there is a [ Indiscernible ] the committee would be meeting on a regular basis to look at even if the study is not unblinded to the data monitoring committee they would say arm one and arm to not knowing which one is which and what have a better look at this. I'm not clear what went on here that this continued for this length of time. I'm not sure.

It is equally disturbing for you as it is to make? Nemec oh was disturbing for everyone involved. This was a complete shock because first of all people felt that why did you can have a placebo on here it is so obvious drug would be so much better so this was the rebuttal to the anti-placebo basically. Also in terms of making sure that there was an interim look at these arms because you are exactly right, you could argue may be at a 50s they look pretty close by the time you get to 100, 150 does clear that those two arms are separated.

Thank you. Appreciate your good work.

Diane?

Thank you, very helpful presentation pretty touched upon the importance of conflict especially with the principal investigator that there can't be recruitment from the principal investigator. Was response to the data monitoring committee, this is funded by the sponsor can you please speak about how attentional conflict is determined within this process? Nemec --

Yes. It is typically self assessment. For example, if I were in a data monitoring committee and I were doing consulting work on a certain drug then that would need to be stated outright that I have a conflict, I am receiving money or I'm working on a clinical trial with the drug acts but we are studying drug Y which is not drug acts or not similar to drug ask. Is more self reporting than anything practice does get to be really tricky because you want to have people who are aware of what is going on in research. If you push the conflict of interest too far to the point where people would not be -- would not clearly understand what is going on scientifically then you do sort of get into this quandary. In terms of excluding too many people. It is clearly self-reported and if a person on the data monitoring committee is doing work that is in conflict in any way whatsoever in terms of the therapeutic area, the drug, the sponsor then he would be excluded from any discussions of that clinical trial.

Thank you.

Diane?

Thank you very much. I have two points, one, there is this [ Indiscernible ] clinical design for trials that is a different approach but it is in theory more efficient when it works and what trials it is appropriate for or not. We have had some presentations by people presenting that the [ Indiscernible ], think that is when it you pronounce it --

It is very interesting such as the play the winter.

You know things Denning you delimiting spray quickly. It is a well-known phenomenon and in some conical trouser doing a pretty FDA is not prohibiting this it would just seems to be something that is a good road to go down to make a clinical trial more efficient.

I agree completely.

I have another question which you may not -- you have been in enough trust you probably know. Clinical trials like to have this -- this is where patients go with a looking for clinical trials for a particular drug or condition. There are zillions of them out there that are completed but no study results have been released. Is there a rule or something that says, between the time you finish the study and anything else happens you have to release your results?

Yes, the have 12 months between the end of the study and to results released on clinical trials.gov at least in a rudimentary way. Yes I am an IND holder so if I get frequent updates from Google trials.gov so if you've submitted something to clinical trials.gov they know when things are do and not do. You have 12 months to put out some updates of the study.

Who enforces this? Does the FDA enforces or who?

That is a good question. Clinicals -- critical trials.gov is the library --

[ Indiscernible - multiple speakers ]

When you sent for clinical trials.gov and you are the owner of whatever clinical trial, the tendencies come to, whoever the IND holder is. Or whoever has submitted the data to clinical trials.gov.

Does the FDA enforced the people put up -- we have plenty of trails that are negative and they never get published. The results never get put up. For obvious reasons.

I do not know the answer to that. I know that --

Who enforces this rule that you just needed to make? Nemec my understanding was that it was --

It is my understanding that it was critical trials.gov. Specifically for that is or aside from the national Library medicine to be honest I'm not sure.

I do not think that they have any enforcement capability. Maybe someone at the FDA could answer this for a some time.

Diane this is Andrea I will look into to get back to.

Thank you. Thank you for your presentation.

Sorry that a do not know the answer.

Eric?

Thank you so much for your very informative presentation. I am a patient representative in the area of pediatric and [ Indiscernible ] disease. My question Pacifica goes back to your phase is slidably the slide number five which talked about the till trials to prove efficacy and safety. I question is, how me pivotal trials must be completed in adults prior to performing the first pediatric trial for medications?

In order for a approval theoretically there should be two pivotal trials in adults is you don't. The conditions, a lot of this is up for negotiation with the FDA review division. There are new laws in place, the best pharmaceuticals for children's act is now permanent at FDA, created is now permanent at FDA so there are discussions fairly early on I believe after phase 2 although we could be off base here about the discussions with the FDA about when to start the pediatric trials.

And some of these conditions, rare but possible there are only pediatric patients, not adult patient so that would flip the other side of things. I believe that there would need to be assured that there is a fairly good safety signal in adults before going to children.

Thank you. By the way the pediatric child's network which you have instituted in which INH does is wonderful in the -- the expense went back to an earlier question of the studies.

Thank you for mentioning.

Jim?

Gentoo, thank you so much. I really have a biostatistical question regarding patient randomization. One of the most significant questions, will have three or 5% of adults agreeing to cancer critical trials that patients do not want to be randomized. My question is, how can we change trial designs to account for potential ideas which would occur if we allow patients to choose their own armed? How can we alter the design of the trial so that patients can choose which arm they want to be in?

That is an interesting question. I couldn't find the site but there is another slide that would be a bear image of that [ Indiscernible ] trial showing the nice survival rate in children and it is simply not the same in adults. Series are asking the question is a lot of the reason seems to be that those resistance on part of the adult oncologist or in the patient population to randomize. I think a lot of this is a mindset which is a real shame. That first light about the New York Times and the negative clinical trials of that was really interesting because just because you have a negative trauma think this came up in one of the other questions, that is not a bad thing. Now you know not trade for either of those things, that is okay or you know that be is not better than a prick that is fine. You've answered a really good question years you can ignore that drug and move onto another one. I thought the I spy breast-cancer trial design was nice because you're not stopping and starting and stopping and starting. You are starting and then doing multiple in terms analysis to see a patient's are doing and then moving through a series of drugs fairly quickly. What is your take on this? It to fill that oncologist perforated or -- the thing about [ Indiscernible ] obviously is a because they're only 12,000 new cancer diagnoses eight children a year it is really forced the pediatric oncology community to realize that a golden opportunity to make something out of this small population.

When an adult has a cancer that had a for a while, they have at the time to study it, to be knowledgeable [ Indiscernible ] answer. The have their thoughts and their ideas. Whether they are right or not, and they often want to choose which arm. You want to choose their treatment because they have studied it enough to again, whether there right or not they feel like they have been arm in mind. One of the to arms is better for them. It seems to me that if they are agreeable to follow all of the requirements of an armed that they should be allowed to be put into the arm by their own choice rather than a flip of a coin.

In other words it would be sort of the reverse randomization?

Patient choice randomization.

Right. That is very interesting. What are your thoughts on that? Do think that is a doable thing?

I have been advocating that for years and years.

Very interesting. I do not know what the take of the adults oncologist would be with that. I'm trying to think -- ischemic the problem is in the adult oncologist the problem is that the biostatistician says they come in no we cannot do that, that would be bias and they refuse even give any consideration.

Typically if a physician makes a determination and there is bias there because the physician feels that for one reason or another should be one or more of the other but I hate the that is an interesting question. I will run the by some oncologist that I know prick I am struggling here to find a flaw in their.

As long as everything is accounted for at the end of the day that you stratified by age and by disease and so on, as long as you are feeling in the boxes it seems like you would not be unreasonable.

I agreed interesting. Thank you.

Mark?

I am wrestling with the Jim's question. Jim maybe we should trade e-mail sometime and talk about that.

What are your thoughts? It is interesting.

Is a very interesting question and I understand his frustration with some of the biostatistician's. It is a complicated question. One of the reasons that clinical trials need to be done is to test people's preconceptions and randomization actually is a very powerful tool for trying to neutralize that. Jim's -- actually out of the dialogue between the two of you you did point out that Jim's a case wouldn't be that different from what is done sometimes in trials where one of the arms is going to be physicians choice. When looked at it that way, this is more intriguing question to try to differentiate.

It is for interesting plus the fact that so many of the phase 3 trials fail given the best of circumstances because the drug simply didn't work. Especially in oncology this particular whether it worked or it didn't so it is not a soft endpoints.

Know that is really -- I don't think that is really the case. Maybe I'm going from the highly selected sample of oncology drugs that end up at the DAC and I know that the FDA seeks advice from the advisory committee in the closed calls. Frankly, and I have been going to those meetings we do regularly for over 10 years now. Sponsors get into trouble there because there is not a clear signal about whether a drug was working.

There is an argument to train whether it is like the overall survival, event free survival.

A lot of this even as to do with how they're trying to measure -- snack [ Indiscernible - multiple speakers ]

Frankly, if there were a large enough [ Indiscernible ] size you would not have those arguments. This a cookie to a whole other conversation, it is kind of getting a little far afield. I do have one observation about your earlier discussion about the conflict of interest. Your point about not wanting to restrict so much that you don't have people in the field ding able to participate. That is a very legitimate concern and it is -- the real difficulty there is that it actually gets beyond the issue of who might have financial ties that potentially could be a conflict. What a lot of people lose sight of the fact is that in addition to financial conflicts there are intellectual complex, that can be just as real and just as potent as any financial ties. Your example here about the arrhythmia trial I think is a perfect illustration of that, the way you described it initially people just assumed that there would be not even any point in having a comparator or even in doing that trial. That is their intellectual bias that is getting in the way their. Then they do the trial and find out they were completely wrong. It is not as important as trying to avoid the problems that can come from doing clinical trials because of financial interest. The whole issue of [ Indiscernible ] boils down to what people's intellectual conflicts actually are going to be.

That is a good way to put that.

Enough of that.

Thank you. These are interesting problems because people do have a point of view.

That is correct. They do.

Sharon?

My question follows up on the question from Diane about the negative trials. I was wondering, you are talking about the a dev diff critical trial that when there would be a point in time that they would go in and look at -- analyze the prior data. My question is, is that data then the reporter how was it reported in the final phase of the trial or is the first part of the trial is that data just set aside or is there a location line in the reporting of that data?

Been looking at the interim analysis in other words?

Yes.

Unless the trial has stopped, typically the trial, the end result take ends up getting published.

At that interim analysis would that data be included in the final report?

I would imagine so. I will have to dig around and see if I can find an example of this.

My question is, and my interest is the first phase of the trial, the first segment of the trial, that data is it forgotten or is it laid aside and then from the interim analysis, from that point forward do they publish just on the data from that point forward?

I'm not sure because the first set of data is obviously completely integral to the design of the second part of the trial so it would have to be in there somewhere. To be honest I would have to dig around and see if I could find an example of what is being reported. There was a famous trial called the play the winner trial. He was looking at [ Indiscernible ], membrane oxidization, just like the poster child for this particular thing, you have a certain number of balls. Somewhere read, some are blue. Every time somebody did better on the red as opposed to the blue they took out a read and put in a blue or the other way around. What ended up happening is that the end of the trial, one child ended up not getting [ Indiscernible ] and the vested in it was not possible to do any kind of statistical analysis on that because of the imbalance in the arm. That was reported because it was [ Indiscernible ]. I would imagine that both would be reported, that we noticed at the end of the plan in term analysis that X was winning over wise so therefore we made a change. I would imagine that that is reported but let me look around and see if I can find exactly what is reported.

Thank you. Very interesting talk.

This is Andrea, how many questions do have been DQ? I noticed that we are 15 min. over and I do not want to take up over -- Dr. Zajicek afternoon and I know others have commitments.

I have four questions (

Dr. Zajicek it is really up to you.

Go ahead to.

If folks cannot hang on you could listen to the rest of the questions on the replay the we will continue.

Judith?

Thank you for the interesting talk. I was interested in the bias that is entered into the studies due to the acceptance criteria. From that, I will give you an example. With a pulmonary fibrosis, typically to BNA trial you have to have a longer biopsy showing that you have IPS period overview or lungs allows enough they do not want to do a lung biopsy on you. Really what you're trial is showing how a subset of people who have not to battle belongs react to a drug rather than if you have -- when I say lousy, you can still be functional, running around doing stuff but they did not want to operate on you.

Right. Interesting. So that would certainly bias the results as your sink towards people of less severe disease as opposed to more serious.

Exactly. A kind of worries me with all the imagination I go into about these means about the statistical significance of this, that and the other, you're leaving out this great big chunk of who got entered.

That is registering. What would you propose for example of the drug unapproved of the and in the phase 4 criteria come or phase for safety surveillance that they look at in registration trial?

Yes. I can -- I'm trying as a mathematician so I really understand the problems that people get into with these things of wanting everything to be comparable. Unfortunately with human beings they cannot be. That is that the basic problem. I would think that you could have something where you have super comparable sayings that you know exactly what is going on but also let other people in and see what happens to that arm. Your example about endpoints with the 6 min. walk test. That is a real good example because I am always saying, why don't you all do a 6 min. walk on these people.

As a biomarker.

Yes. Because is one of the few ways that you can tell that they do things like number of hospitalizations. As a patient you would rather be able to walk 6 min.. As a patient you would rather be able to walk 6 min. I would be in the hospital one extra time a year if I could walk the 3 miles frankly. I guess my suggestion would be to have another group.

[ Indiscernible - multiple speakers ]

You can kind of keep them separate.

I do not think that as a result. It of the was he of the people I could have the biopsies and the people that couldn't in and have some other biomarker of [ Indiscernible ] diseases being the third category.

I see your point because you are taking out the people that can probably is a more than the other people.

Thank you.

Paul?

Andrea when you respond to the question on the one-year deadline for publishing results and the enforcement aspect of that, could you publish that to all of us participants?

Absolutely.

Thank you.

Jim?

My question has to do with your opinion of crossover. When we have had these double-blind placebo-controlled clinical studies and the endpoint is survival, it's such an ethical questions of these men would have to get into a control group where they would not be getting a treatment and the only way they would contribute to the studies they would have to die. How does crossover of fact a statistically the ability to prove the efficacy and safety of a drug?

Is simply the most beautiful thing because you are being used as your own control. The only issue there is the carryover effect and I guess that is the problem with the crossover is you are concerned that you have got a in the you have got be in other people got the and a. The people that got a first are doing better so if they got a first, was very carryover effect? I think the carryover effect is really the problem that comes up with that trial design that is seems that you would be very clean because then you would act as your own control. You would've had both treatments and then you would know which ones worked or did not unless there is carryover.

It did increase the number of people who would apply or agree to be in the clinical studies one there was a possibility of crossover.

I consider because people do want to get something, hopefully it is not going to wind up with the CAST study were you got something -- people to opposite want to be treated but the thing about, at least for the -- you are never going to get nothing. If there is a standard treatment for something you will get something.

In other words you could to the active comparator the standard of care plus something or plus nothing see we have gotten at least the standard of care as the background.

Thank you.

Rapacious concerned they were getting no treatment?

And they get a placebo, the placebo is just defined as not getting any particular treatment.

Right, but they would be getting something. It wouldn't be nothing against something it would be two arms of the same thing on either side and you'd be adding something. Were they never getting -- these are people of prostate cancer you said?

Yes.

And at one point did be getting no treatment?

Correct.

That seems peculiar. Because there was no standard of care?

When you have exhausted the chemotherapy at the time there was absolutely nothing left the experiment to group did have a treatment and the control group there was nothing left.

That it's. Understood. No radiation? Fact that our to been exhausted.

Okay.

The crossover made a big difference in their willingness to participate in a study.

Right. That makes perfect sense because most people who want to try something.

Was that design declined or was it successful?

When they began using the crossover is when we saw additional volunteers are dissipating in the clinical studies. I just wondered statistically whether or not the industry or the sponsor would have any more difficulty getting it approved by the FDA.

A Vonage of the hundred of the carryover problem or the order of fact I think, cannot see why that would be a problem but again I do not work for FDA so I do not know. It was really the carryover that seems to be the problem.

Caroline?

I am the newbie so this may be a question that should know the answer to but with the block randomization, do you typically use that to separate your different age groups or other types of patient subpopulation?

You could do for pretty much for anything and in the case of this, we had used it for randomization by site and by drug arm and by age. There were for ages so there was the incident, the young child come the older child in the adolescent. That was the reason that we use that and wanted to see if there were different effects by side, age, drug. Reaser present reason.

When you analyze the data, to look at all children and then each of those subgroups?

Yes. We're in the process of doing this I cannot say anything useful about the results But yes, when they were lucked out by age, site, drug, exactly, everyone together pulling them apart, see the beta difference one way or the other so it is being looked at it always.

So there is no cost in terms of the power of the study?

There was not a cost in terms of the alpha exactly because when we looked at the results of the interim they were not unblinded. If you start on blinding things in the middle of the test that is a whole other issue as you are pointing out that you may have to come I didn't going to this but you may have to increase the patient number if you unblinded but we did not unblinded. We were just looking at [ Indiscernible ] without looking at [ Indiscernible ]. That is an issue the start on blinding in the middle that you will change the statistical power.

That is on blinding to the investigators or just the [ Indiscernible - low volume ]?

Definitely not for the investigators unless there was a problem. This would be for the statistician and the data monitoring committee.

This gets endlessly complicated am not a set addition to going to the numbers here but it does affect the number, the power.

Setting up the design with block randomization's is not diminish the power per se --

That is my understanding as. It did not. It clarifies what could be contributing factors to a result like if there is a side effect, is that the drug or was it the fact that the six the ¬6-¬9 did much better than anybody also the FDA was interested in knowing the sub categorization of the patients and whether one group responded better or differently than and other group.

Thank you.

I'm showing her for the questions at this time.

Thank you for hanging in there Dr. Zajicek and everybody else. I know it has been way over our time, so thank you so much for a great overview of clinical trials. This information Dr. Zajicek is reported for patient reps to have when they're serving on FDA meetings and has been very helpful. I think everyone does is been a fabulous dialogue discussing clinical issues but clinical trials. Any final comments Dr. Zajicek Just when going back type question think it was by Diane about the negative trial stopping published practice is an ongoing problem because people like to read positive results, the thing the negative results are born but they're not boring because that is the whole point. You did a trial and you have one arm that did not work then you shouldn't be writing for that are many more. It really does biased literature when you're looking for something and whether something worked or didn't work. All you are seeing are the positive results in it is a problem. As part of the, not to to my own horn here but part of the best pharmaceuticals for children act of the clinical trials that NIH is doing, the data will be and are -- will be public we available sued we want people to look at the trouser we have done or go into the get it by data set and do a secondary analysis. This issue the negative house and the availability of the data is an ongoing issue.

Thank you so much. I think everyone for joining today. I apologize for the length of it but you could always jumpoff at any point but just remember that for the future and the replay what was be available if you want to do some further. Thank youDr. Zajicek and thank you everybody for joining us today. Have a wonderful afternoon.

Thank you so much. Goodbye.

Could buy.

Thank you. This concludes today's conference you may disconnect at