For this time.

So we’re (presenter muttering indistinctly)

All right, so hey, everybody, welcome.

Today’s my privilege to introduce Dr. Glen Laird. Dr. Laird earned his PhD in statistics from Florida State University in 2000, then worked as a survey statistician for RTI International before joining the pharmaceutical industry where he worked at Novartis, Bristol Myers Squibb and Sanofi. And so now, he’s at Vertex Pharmaceuticals. And so let’s welcome Dr. Laird.

I hope everybody can hear me also online. I hope we can have a good discussion today. Have a lot to talk about. Feel free to interrupt me at any time with questions.

There’s really nothing overtly technical here, so I wanna be very accessible to everyone. I’d like to hear your feedback go along. So I’m gonna be talking today about industry-sponsored clinical trials that is pharmaceutical industry sponsored trials.

So disclaimer, I work for Vertex, but any opinions are mine, not theirs.
So for a clinical trial, you’re gonna have a clinical trial team, right? At Vertex, we call it a study execution team. Other companies call it something different, but it’s the same kinda thing. It’s a group of people who are responsible for running, conducting, executing the trial. It’s gonna vary by the study, but usually, this is gonna include a clinician of course, who’s gonna make the key clinical decisions about the study.

An operations person’s gonna do a lot of coordinating with the site, a lot of communication with the site. Also shepherding documents through reviewing, things like that. Clinical pharmacology, they deal with pharmacokinetics, which is how the body processes the drug. metabolism, that sort of thing. Safety, at some point, FDA let it be known that they wanted you to have a person explicitly responsible for safety on your study team, so. Because then, I think there was kind of a mindset that if you had the same person trying to look at safety and efficacy,
that they would probably end up spending most of their time looking at efficacy. Safety might not get the attention it deserves, so you have to have a person explicitly for safety.

Clinical biomarkers, we often like to look at a lot of different biomarkers.

Data management deals with the actual database itself, setting it up and the sort of execution around locking it and all that sort of thing. And cleaning the data.

The statistical programmer is responsible for a lot of the actual execution of the various plans, right? So, and, of course, the statistician, which I’m gonna talk a little bit more about. The statistician and the programmer really work kinda hand in hand for a lot of things, right?

There’s a lot of things where the statistician is planning things, specifying things, and the programmer is the one writing the code to actually execute it.

FYI, so what I just talked about was a study level team. There’s also a project level team. So by project, I mean a drug or a therapy, right?

So there’d be some more senior people.
So there would be like a project level statistician and a team at the project level with a lot of these same similar functions plus some others. Legal, for example, comes to mind. That project team kinda guides the overall development of the drug. But today, I’m gonna focus more on the study, what the statistician and that team is doing. A lot of you may know this, but there’s four sort of commonly recognized phases in drug development. Phase one is mostly about safety. You’re trying to find the right dose of the drug. Main purpose of that is to convince yourself whether you want to do phase three, which is the pivotal study, the main bulk of your evidence that you claim to submit, to say, ”Here’s our evidence that this drug works.” That study is often the biggest and it’s generally randomized, right? And then there’s phase four, which would be anything that’s post-right, and those kinda studies can depend on the market conditions for your drug
after it’s gotten on the market.

I’m gonna focus the most on the phase two, three type studies 'cause that is sort of the most classic clinical trial experience. And it’s perhaps the part where the statistician and the programmer are really the most key to being and their involvement.

That is the scientific rigor of actually demonstrating this drug works.

As I noted the bottom there, the great majority of drugs that start in phase one end up dying somewhere along the way unfortunately.

You can look up various numbers, but it’s a pretty small percentage and actually end up making it to the market, unfortunately.

from direct to start in phase one.

Oh, okay. All right, so now we’re at the survey here. Alright, so all right, then. So then. This is my survey question, hope everybody. Oh, and then just hit present. And then I need to do this, so, okay. So I’m wondering what you think.
130 00:05:59.580 --> 00:06:04.580 So when in the life of a study do you think is the most work
131 00:06:05.280 --> 00:06:06.423 for the statistician?
132 00:06:07.560 --> 00:06:11.553 So if you can’t see there, so option A, these plots are qualitative, it’s conceptual, right?
133 00:06:12.420 --> 00:06:15.510 So the x-axis is time,
134 00:06:15.510 --> 00:06:17.910 the y-axis is the amount of work, right?
135 00:06:17.910 --> 00:06:19.830 So option A would be level, you know? It’s basically the same amount of work over the whole course
136 00:06:19.830 --> 00:06:23.370 of the study from when you first start conceiving the study
137 00:06:23.370 --> 00:06:25.680 Option B is going up and up and up, the longer the study goes on.
138 00:06:25.680 --> 00:06:28.450 Option C is the opposite. Start very busy, gets less and less busy.
139 00:06:28.450 --> 00:06:30.660 until you rep the study before, right?
140 00:06:30.660 --> 00:06:33.360 Option D is Gaussian looking, right?
141 00:06:33.360 --> 00:06:34.800 And E is kind of the opposite of that.
142 00:06:34.800 --> 00:06:36.720 A lot of work at the beginning and the end,
143 00:06:36.720 --> 00:06:40.083 maybe a bit of a lump.
144 00:06:41.100 --> 00:06:46.100 So I know people know how to fill this out or.
145 00:06:46.230 --> 00:06:48.330 There’s a bulge of work in the middle.
146 00:06:48.330 --> 00:06:50.100 And E is kind of the opposite of that.
147 00:06:50.100 --> 00:06:52.410 A lot of work at the beginning and the end,
148 00:06:52.410 --> 00:06:53.510 maybe a bit of a lump.
149 00:06:55.770 --> 00:06:59.430 So I know people know how to fill this out or.
150 00:06:59.430 --> 00:07:00.360 <v - >Yep, text.</v>
151 00:07:00.360 --> 00:07:01.650 <v - >Whatever.</v> <v - >Get our your phones,</v>
152 00:07:01.650 --> 00:07:03.485 which you don’t hear often.
153 00:07:03.485 --> 00:07:05.203 (Glen laughing)
154 00:07:05.203 --> 00:07:06.036 <v - >Yeah.</v>
155 00:07:14.040 --> 00:07:15.993 People online, I hope, are voting too.
156 00:07:20.340 --> 00:07:24.903 When do you think the most work is?
Most people answered D.

Maybe I don’t know how to tell how many people,

I hope it’s more than. Yeah. (laughs)

I hope it’s more than like six people that are voting.

I feel good when you see some prime numbers and stuff in there, it makes you feel like, "Okay, 10 must be big enough that you’re getting something."

But, okay, so it looks like most people say D, fair number of people say E, now, it’s not a lot for the other choices.

Like so do I just go back? Yeah, you just go back

Do I just hit escape? Escape.

Present mode.

It’s not working?

That’s it? Yeah.

I think we’re out of present mode though.

Yeah.

There we go.

So in my opinion, I think most people would agree with this.

I would say the answer is actually E, the opposite of what most of you picked.

And the reason for that is there’s a lot of stuff
the statistician has to do at the beginning of the study in terms of planning, specifying what kinda study are we gonna do, how are we gonna plan all kinds of stuff. I'll talk some more detail in just a minute. And then there's a lot of work reporting at the end of the study executing everything you said you were gonna do, right? And it's not uncommon that in the middle maybe there's a bit of a low where you're mostly kinda waiting for patients to enroll and everything is maybe blinded even. So you don’t have it available, right? So what does the life of a study look like and what is the statistician doing during this study? So I'm gonna give you an outline. Again, it’s just main steps. Don’t take anything here too literally, this is just kind of my ballparking of things, way things tend to go at most companies, but companies in general are more alike than different. A lot of this process is actually quite standard. They just have little different flavors, you know, different tweaking of the timelines and such. But the general idea should be pretty consistent.
This isn’t covering special studies, targeted study. I’m talking about a sort of a classic, you know, phase three type study here. You wanna move that window? Yes. I’m sorry. Thank you ’cause I’ve got that. I know it’s hard to figure out. Stuff I want to, yeah. So the first thing you notice here is that there’s tons of acronyms, right? That’s part and parcel in the industry. There’s a lot of things here. But that right, I’ll go through ’em. So the first thing here starts with protocol concept, right? So the protocol concept is basically a document that just gives you kinda the bare bones of what do you plan to do in this study? What’s the disease? What kinda patients do you plan to enroll? What are you gonna measure on those patients? When are you gonna measure it? A little bit about how you’re gonna analyze it. And, of course, the sample size, right? Which the statistician has to calculate how many patients you’re gonna study, right? That gets reviewed by various functions,
including, of course, biostats. And also gets reviewed by a PRC, which is a protocol review committee. And oh, they got blocked out a bit there. So FSFV is first subject, first visit. If you’re studying patients, you often say first patient first visit. So those are really the same thing, just depending on whether you’re actually studying patients that have the disease or just healthy volunteers for example. And so this gets reviewed by the protocol review committee. Again, that’s one of those things that every company’s gonna have one or more protocol review committees, but they’re all gonna be, and they’re gonna have a little different flavor. But it’s gonna be pretty similar. So if it’s approved by the PRC, then you come back maybe two, three months later, say, with a full protocol, which should be very similar to the protocol concept. You’re just filling in more details of how are you gonna measure these endpoints, for example. You know, details on inclusion and exclusion criteria for exactly who gets in the study, some things like that.
Still doesn’t have all the statistical details in it, right?

Has some high-level summaries of what kind of analysis you plan to do.

But it’s not table shells, it’s not the real statistical rigor details.

So let’s say that gets approved by the PRC.

Now I move on to case report forms or CRFs. Those are the actual forms where the site enters the data, right?

So principle here is the sites enter the data, the sites change the data, we don’t touch the data, right?

We just talk to them about how they’re supposed to do that, right?

We don’t touch it, we just query them and say, "Hey, do you need to change this data?"

And then it’s up to them to change it.

So it’s important, this is a process not driven by biostatistics, right?

Operations and data management, run it, but it’s important for the statistician to be there.

Because if you don’t have a good case report form, you’re not gonna get the data you need, right?

You’re gonna be in a bind at the end of the study when it turns out the form didn’t collect what you wanted to report.
Similar to that, there’s edit checks. So edit checks is something to respond to the site whenever they enter something that is questionable, right? The site enters that the patient was 200 years old, that’s gotta be some kinda typo. It’s gonna immediately spit up something saying, "Hey, double check that number, right?" So edit checks are important in terms of getting good data in the system in the first place, right? In the real world, things don’t always go according to the protocol, right? There’s often missed assessments, assessments that weren’t done at the right time. Patients that were enrolled that actually weren’t supposed to be enrolled according to the infusion criteria, various things in the real world may go wrong. And so the statistician plays a key part in specifying what you’re going to do about those, right? This is before you’ve enrolled anybody. You’re planning, okay, we can foresee that this may happen. What are we gonna do about it?
You might have a, you might say, if patients are not enrolled, if patients are enrolled who don’t have the treatment history we intended, then, for example, you might say, "We’re not gonna include that. We’re not going to include that patient in this particular analysis.”

Might be one thing you would pre-specify about how are you gonna handle that protocol deviation, right? The randomization request. Every company’s gonna have a form the status session fills out to say, "Please do the randomization in this way.” We almost always do some form of stratify block randomization, right? So anybody who maybe doesn’t know, right? A block is a small sample size where you know the randomization’s gonna work out even, right? So if your block size is four, you’re guaranteed that two of those four are gonna be treatment, two of those four are gonna be controlled, right?

It’s just a matter of which two bits the order. So that helps enforce some balance, right? And then we’re gonna have stratification factors. Those are often a common topic for discussion.
and exactly what are we gonna stratify for the randomization, right?
So a statistician’s very important in making sure and figuring out how that randomization is gonna be done and filling out the form properly, right?
The data monitoring plan, that’s more driven by data management, but the statistician needs to look at it.
So the monitoring plan is like how are we gonna look at the data in an ongoing way during the study, right?
So if say sites are not understanding the protocol, they’re enrolling the wrong kind of patients, you wanna catch it as soon as possible, right?
So you’re looking at baseline data, blinded data, and trying to see if there’s problems that could affect the scientific validity of the study.
Okay, then just, there we go. All right, so during the study, I have the red box here around finalize the SAP, which is the statistical analysis plan.
This is the single document that the statistician is most responsible for.
And that’s the document, statistician authors it,
facilitates the review of that document. This is the document where you do put all those details, all the statistical nitty gritty details about how are you gonna handle missing data? How exactly are you gonna define the baseline? What are you gonna do? What covariance are you gonna put in your model? All these kind of details about exactly how you plan to do the analysis, right? And this also gets reviewed and approved by all the usual review machinery in the company, right?

So notice about the timing. So if you have a unblinded study, you need to do this before you enroll anybody, right? Before first patient, first visit. If you have a blinded study, it can be done somewhat later after you’ve started enrolling patients. You still need to do it in time to allow programming.

You can’t do it at the last minute, but you don’t have to do it before you enroll a patient. Does anybody have any idea why that would matter?

Whether it’s a blinded study or not on the timings?
Somebody who doesn’t have sandwich in their mouth, perhaps.

(attendant chuckling)

You have the big rooms.

I highlight this because this is another very important principle of these studies, which is pre-specification, right?

Things that you say and do after the data are known, after you know who’s and what treatment group

are considered post hoc, right?

And they’re going to be viewed, I’m not sure if suspiciously is quite the right word,

but are gonna be viewed with additional skepticism, right?

So before that, you start enrolling patients,
or before the study’s unblinded,
you can still claim that you’re pre-specifying things.

Hey, when I said we were gonna do the analysis this way,

I didn’t know that this patient was in treatment

and that patient was controlled, right?

So you could still claim to be even handed

when you do the plan.

Then I’d say maybe comes the lull

I was talking about, right?

Maybe in the middle, yes, you’re executing the data,
monitoring stuff that you said you were gonna plan.

That’s not really heavily driven by stats.

There’s always gonna be team meetings. It varies, they might be say monthly.

A lot of that is kind of study status things on enrollment and discussions about whether we need to do an amendment.

So maybe there’s a bit of a lull there.

Towards clinical database lock, which is what CDBL is, right?

Now, you want to do dry runs.

So by now, programming has done the programs you want to execute those programs on some version of the data in order to see whether there’s, you know, issues at the tables look fine.

So a lot of times when people do the blinded study

is you’re gonna use dummy codes, you just make up false treatment assignments and you stick that in and then you run the table and you just kinda see where they’re fine.

Then you have to identify the protocol deviations.

This is the part where, remember earlier you were planning
how you’re gonna handle the deviations. Now you can get close to database lock, you have to execute that. You have to apply it to the actual data and say, "Hey, just looking at the baseline data, I still don’t know who’s treatment, who’s control.” I’m gonna say that patient is not in that analysis because of the rule I said before and I’m doing this now before I know, right? So you have to do that kind of applying it and you have to sign off on that saying, "Here’s the official call of who had what deviation.” Then at the database lock, there’s all the reporting stuff. You fill out a form to unblind the data. Usually very quickly, within a week or two, you have to deliver the key results. Vertex would call it the key reports memo or KRM, other companies call it something similar. But basically, within a week or two, management’s gonna wanna know kinda the bottom line, right? And was the p-value less than 0.05? Was there some kinda major safety situation we oughta be aware of? That kinda thing, right? After that come the full list of tables, listings and figures.
And then you have to finalize the clinical study report for CSR. And for that, you would have to author, you know, the statistical section of CSR. So that is kind of an overview of this is what a clinical, you know, study sort of looks like to a statistician and how you're doing, right? I'll note that it does vary some by the phase, right? To me, phase one, it's more exploratory. It's often unblinded. There's more kinda going on during the study 'cause you don't really understand the drug yet, right? So there's amendments maybe more common, I think of it a little bit more like drug babysitting, you know? You're kinda like, "Okay, what's gonna happen today, you know, with each new dose that's going on?" So there's kinda more work to do during the study. People don't worry as much about the planning 'cause everybody knows it's exploratory, right? Phase three is kinda the opposite. Everything I just said before, lots of planning, you know? Lots of trying to pre-specify things.
Even things that are maybe somewhat unlikely,

you know, very rigorous, right?

It’s ’cause it’s often a very big study,

it’s very expensive, it’s very costly,

and a number of ways, if it fails, it’s gonna be, you know,

it could be pretty bad for the company depending on the situation, right?

But the point is you have to carefully consider,

you know, the details.

There’s more attention, more review by both management

and, of course, health authorities like FDA.

So for phase four,

there’s a group often called Global Medical Affairs.

There’s another group called Health Economics

that often deal with these kind of studies.

You can often look at longer-term safety and efficacy.

They may address reimbursement.

So reimbursement is kind of a bigger deal in Europe

because they have single-payer systems.

And so just because you get a drug approved by the EMA,

which is kinda their version of FDA,

that means you can sell it,

but that doesn’t mean

the governments have to pay for it, right?

You have to make a separate case to them to say,
"Hey, not only does this drug work, it’s actually worth what we want you to pay for, right?"

There’s a negotiation there.

There gonna be a lot of publications involved in this.

I don’t know if you’ve heard the term real-world evidence, or real-world data,

but this is being used more and more in phase four.

Once the drug is on the market in the real world,

there’s data related to that.

There’s insurance claims,

there’s electronic health records,

things that weren’t around back when I started, right?

That can help you understand what’s going on

in the real world with your drug.

And these are often very big datasets,

but they can also be kind of messy in a lot of ways.

Sometimes, there’s a specific group for real-world evidence,

that group is closely aligned biostats.

Vertex has a group called

(Glen muttering indistinctly)

which is statisticians who are kind of particularly knowledgeable about dealing with these kind of data.
People sometimes ask, "Well, what kinda statistics do you use?" Not really a good answer to that. It varies a lot by the disease you’re using, by endpoint, I mean, variable, the outcome that you’re measuring there. So it depends on the challenges of the setting. Like maybe sample size is a big issue, others may be missing data as a big problem. I used to work in oncology before I worked at Vertex. They use a lot of time to event endpoints, like time until the disease progresses. So they do a lot of survival analyses, right? Vertex, we don’t do oncology anymore, so we have some time to event endpoints, but not that much. So the point is it just kinda depends on what you’re studying. But, you know, companies understand that, you know, people aren’t gonna necessarily walk in the door happening to be specialists in the exact kinda statistics that we’re using right now. So, as an example of it depends on the setting. Vertex does a good bit in rare diseases. So I thought I’d just highlight a couple things about rare diseases. I’m not gonna go through all of these, but just in general,
kind of the understanding of the disease and rare diseases can be limited. There haven’t been a lot of studies conducted on this before. There’s often not a lot of good prior information. Identifying patients can be difficult. You don’t often get enough small sample sizes because there’s not a lot of patients out there. A lot of these diseases are congenital, right? They’re genetic, you’re born with ‘em. So a lot of the patients, I’ve read more than 1/2, are actually children. So, you know, that creates a whole nother aspect to the study if you’re trying to study this in a child. A lot of use of innovative study designs, adaptive designs, things like that. Maybe I’ll talk a little bit more about that, and a lot of use with biomarkers and modeling simulation. If you wanna know more about these sorts of things, I’ll give you a shameless plug for a book. I’m actually not one of the editors of this book. These people are my coworkers in our department at Vertex. I contributed to some of the chapters. But I think it’s a nice book.
in that parts of it are technical, a lot of it isn’t, but it is written by quantitative people kind of with a quantitative focus on, or, you know, kind of through a quantitative lens  on what one does and are disease drug development. So that’s my plug. Little bit of organizational notes about how companies work. A lot of companies are organized by therapeutic area and or phase of development. Some companies have an early phase group that sort of all they do is phase one studies and they kinda crank out these fairly standardized phase one studies. Vertex is not that way actually, we just go by different therapeutic areas and have the same people who do the phase one study and the phase two, phase three studies. In general, a lot of companies are more alike than different. We have a similar regulatory framework, right? So like I said, FDA says, ”We want you to do things this way.” So everybody does things that way, right? We have a lot of the same employees. So, again, there’s different flavors of things, right?
Like the protocol review committee, they’re all gonna have one. But some companies might have different protocol review committees for different types of studies, or maybe it’s a little bit different how they set it up or, you know, but it’s largely the same thing. For biostats, my advice would be to inquire with any sort of company you’re thinking about working for or with. I would inquire about the methods group. Why do you think I say that? I’m the methods person, it’s not because the methods group is the most important group, right? Why do you think I would say understand the methods group at whatever company you might be? It’s actually related to what I just said. So maybe to stay on top of the latest trends. So maybe to stay on top of the latest trends. Stay on top of that. A very noble answer and kind of right. A very noble answer and kind of right. (attendant laughing) I mean kind of in the sense that how you do that’s gonna,
you want to do that, but how you do that is gonna vary.
I just said companies are more similar than different,
but your methods group is an exception to that.
It’s actually not standard
and it varies a lot by the company, right?
So I used to work at Novartis, as we told you.
Novartis has pretty much kind of an internal department
of methods that it’s almost like a mini academic institution
within the company
that they crank out academic-style papers.
Pretty large group, quite technical in their focus, right?
On the other extreme,
I also used to work for BMS
back when they had a site in Wallingford,
they had no methods group whatsoever.
You wanna do methods? It’s your job.
Do it on nights and weekends, whatever, right?
So that’s why I mean you’re kinda right in the sense that
if you want to do that, you need to understand like,
"Well, am I gonna be working with something
like the Novartis group
or am I doing this all by myself, right?"
So you might ask a board about me.
At Vertex, I’m neither of those
kind of triangulated to that.
I don’t have a group. I’m a one man group. And so I view myself as kind of a facilitator or a focus kind of person. So if people are interested in doing methods, I work with that person. I’m co-authoring some papers. I try to keep tabs on things that are going externally, that kind of thing. I try to help focus resources and utilize people who have interest and availability at that time. Maybe they’re in that role, you know, as possible to look at topics as I can sense are of interest, right? But my bigger point is it’s gonna depend quite a bit by the company. FDA’s not gonna specify how you use a methods group. Really quickly, people often ask me, "Well, what’s kinda the difference between people that are successful and not?" These are pretty high level, but in general, communication is important, right? Being able to make a point concisely, clearly, being able to communicate with non-statisticians, being able to give a presentation even in front of fairly large group of people and understand and explain your arguments for why you’re doing what you are. Time management, like I said,
there’s a lot going on at a trial, you might be assigned to,
you know, two, three, four, five trials, right?
And they’re all at a different point
in that live curve, right?
And so you need to be able to figure out
how you’re gonna manage your time
across all those things, right?
So, you know, you’re here in school,
maybe you have a job outside, you know,
whatever, at the library, you know?
People here don’t care what’s going at the library.
Library doesn’t care what you’re doing here, right?
So you might have five different studies
and you may have to figure out, well,
I need to do this on this study now,
not because the team’s telling me they have to,
but because I know next month,
I’m gonna have to do something else in another study.
Right, so you have to kinda like juggle
those different time commitments
and that’s something your manager would hopefully be able
to help you with.
But there’s some skill in trying to figure that out.
And just being generally proactive and visible.
You want to,
you wanna be seen.
You know, you can give presentations, staff meetings, there's working groups. I'm involved with that kinda thing, which is kind of like a team approach to research, right? We see a topic that's of interest and we kinda divvy people up and okay, well, you can do the simulation, you go look at the literature. You know, something to get your name out there that people can remember you. But being the methods guy, I thought I should comment at least a little bit on some things I see going on in research right now, what my thoughts on are. There's a lot going on now with borrowing data and using real-world data, right? So people want to do a clinical trial. It might only be a single-arm study or it might be randomized, but they wanna try to use historical data. Sorta combine the two in a way that borrows strength and gives you a stronger conclusion. There's a lot coming out with that now, there's Bayesian approaches. I don't know if many of you are familiar
with propensity score, I don’t have time to go into it now,

but propensity score is basically an approach for trying
to connect historical data to your clinical trial data
and maybe match patients up in ways that are similar as possible.

Right, you often know a lot of things the baselines
that are prognostic for the patient, right?

So you try to make it where you’re as close to an apples to apples comparison as possible.

There’s a lot of details about exactly how you do that I think people can still figure out better and learn more.

A lot of work with adaptive designs.

For example, you might combine a phase two dose selection
with the phase three efficacy part.

So there’s a lot of people looking at that because you can gain a lot of efficiency by not having to do a separate phase two study and sort of start all over

with a separate phase three study, right?

My opinion, adaptive designs is that if you sort of know what you need to do
that is you know your population,
you know what you wanna measure in those people,
you have a decent idea of what your treatment effect may be,
you know, then just do the phase three study you think you oughta to do, right?
If you’re kind of at the other extreme, you really don’t know the answer to much of any of that stuff, then you should probably do two separate studies, right?
Just do the phase two study that’s not pivotal. Learn what the heck is going on and then do the phase three study.
If you’re in the middle, which is you kinda mostly know
what you’re doing, but there’s this one nagging question, I don’t know if I wanna do the high dose or the low dose,
or I don’t know whether the patients need to be, you know, have this biomarker or maybe a, you know, I can do it on everybody, you know?
What population? You have that one nagging question, that’s where an adaptive design can often be helpful, right?
That way, you can build a design around getting information about that key piece and going straight into phase three. A couple things I think are maybe a little bit under-researched, could be looked at more.
I think a single-arm design that can change to a randomized design, stage two,
something I would like to see a better treatment of
because what I was talking about before
with the real-world data,
you’re trying to compare it, right?
That works best in the extreme cases, right?
So if the real-world data say this is what happens

to an untreated patient, right?
You tend to see this sort of result.
If you do a single-arm study in your experimental therapy
and it looks the same, then you have a good answer.
The answer is your drug’s not that good
and, you know, and you’ve done it efficiently, right?
Single-arm study is smaller, right?
If the results are great, much better,
then you’ve also have a good answer, right?
Even if there’s some bias in the real-world data,
the results are so big,
it’s gotta be something good with the drug
going on there, right?
It’s that middle case that’s kind of awkward, right?
Well, it’s better, but it’s maybe even p is less than 0.05,
but there might be bias in that historical data
and, I wish I’d done a randomized study
sometimes what you might think, right?
So then I think it’d be interesting.
818 00:36:48.750 --> 00:36:50.580 you do state choose the randomized study,
819 00:36:50.580 --> 00:36:53.280 you combine the two phases, right?
820 00:36:53.280 --> 00:36:56.820 And then you come up with one result for the
whole study.
821 00:36:56.820 --> 00:36:58.710 And lastly, I’ll mention,
822 00:36:58.710 --> 00:37:00.240 I think there’s more actually to do
823 00:37:00.240 --> 00:37:01.690 with good old stratification.
824 00:37:04.440 --> 00:37:07.230 We’ve had a couple situations where we were
unsure
825 00:37:07.230 --> 00:37:09.270 how to stratify in a study.
826 00:37:09.270 --> 00:37:11.700 We actually had a group go back, look at the
literature,
827 00:37:11.700 --> 00:37:15.840 the literature actually a little bit more thin,
828 00:37:15.840 --> 00:37:19.440 vague and conservative than I thought it was.
829 00:37:19.440 --> 00:37:22.290 If you really want to understand, hey, from
my study,
830 00:37:22.290 --> 00:37:24.843 I’ve got 150 patients, these are the factors.
831 00:37:26.220 --> 00:37:28.620 It not actually specific as you might think.
832 00:37:28.620 --> 00:37:30.630 And you can get into things like whether
833 00:37:30.630 --> 00:37:33.210 the stratification factors are correlated
834 00:37:33.210 --> 00:37:35.043 with each other, right?
835 00:37:36.090 --> 00:37:39.240 And continuous factors you might wanna
stratify on
836 00:37:39.240 --> 00:37:41.040 is another kinda area people could go.
837 00:37:41.040 --> 00:37:43.860 So I think there’s still more to do there.
838 00:37:43.860 --> 00:37:46.080 I say it’s important for small studies, right?
839 00:37:46.080 --> 00:37:47.820 So if you’re doing a big study,
840 00:37:47.820 --> 00:37:49.740 the law of large numbers is gonna probably
cover,
841 00:37:49.740 --> 00:37:52.057 you could probably stratify nothing
842 00:37:52.057 --> 00:37:53.760 and it’ll be probably okay, right?
843 00:37:53.760 --> 00:37:56.490 But studies are getting smaller and smaller,
844 00:37:56.490 --> 00:37:58.770 people are in more and more focused groups.
A small study, if I can say something a little bit controversial, small randomized studies I think are a bit dangerous, right?

People love this notion that a randomized study’s unbiased, but that’s in the long term. I only get one chance to do my study. There’s only 30 or 40 patients in it that might not be big enough to guarantee that everything’s gonna work out even.

So that could be a little bit dangerous. If you’re gonna do it, you might wanna think about stratification carefully.

 Probably already talked to you.

I wanted to leave at least eight minutes. Okay, you’ve got plenty of time.

you’ve got like 10 minutes. you were told like or by 12:50 or whatever.

Yeah, we have to be done by 12:50, yeah.

By 12:50. Right, so.

Question. 12:40, so we got like 10.

Anyone in the room or on.

Yes.

So, okay, I feel like drug development.

and in particular FDA, are pretty conservative with how they like designed their trials,
especially with like phase two and phase three trials.

So again, obviously, you’ve talking about like some of these adaptive trials.
And let’s say like you’re in a company that like has,
I’m not sure Vertex has done a kind of adaptive trial,
not that I’m aware of.
But like if let’s say you thought it’s a good idea for a certain drug,
for a certain program, like how would you go about
like making the case that an adaptive trial is better?
Like obviously, like this is assuming you have like a theory behind it
that it is, for some reason, better.
Yeah, that’s a very good question.
We do have an adaptive study actually,
the one like I had mentioned there
with two different doses, do a phase two,
and then we’re gonna pick a dose and dose into phase three.
There’s a series of meetings.
I didn’t have time to talk about it,
but there’s like type A, type B, type C meetings
you have with FDA along the way.
There’s another type of meeting,
one of them is called the end of phase two meeting.

So you do have meetings at FDA where you can propose things and say, "Hey, we think we oughta do it this way."

As you may have briefly seen on the slide about rare diseases, the regulatory framework on rare diseases is less certain,

which is both good and bad.

I mean, right, it can be bad in the sense that you’re not really sure what you’re allowed to do.

But it’s also good in the sense that it’s more possible for you to argue things like,

"Hey, there’s not that many, you know, say kids with Duchenne muscular dystrophy, you know?"

It’s not that big a population.

These kids have a serious disease.

We need some flexibility in our design to show that our drug is working, you know?

So it’s a little bit easier in rare diseases.

So you could either use those type A, B, C meetings with them and, of course, you’re gonna send them your protocol and stuff to sort of make your case in a meeting. They also have a program called the Complex Innovative Design Program, which is actually run by their stats people.
where you can set up extra meetings to review things like simulations, right? Their biggest concern is maintaining type one error?

So I mean like, so I worked in drug development for the past six years and like interacting with FDA and like FDA minutes and such, like I've seen like them say one thing and then like the next meeting say, "Actually, we change our minds." Or they give like vague answers. And so you like internally have to kinda figure out like what you're gonna do.

So like in those situations, like where okay, like FDA like might be okay, we're not actually sure, like I guess like how do you build like the, and then obviously, the tendency then is to like just go back into just do like what you traditionally done, but like if you like are really advocating for something like this. Yeah, there's a balance there.

It's not uncommon to be like not completely sure what FDA does. I mean if you schedule one of these meetings with 'em, yeah, they will give you a response. It might be in person, it might be written,
it might not be everything you would want to see.
You might still have questions after seeing it.
So it depends.
Sometimes they’re pretty clear,
oh no, we don’t like this or whatever.
Other times, you’re kinda still
kinda scratching your head a bit.
A lot of times, they say something is a review issue,
which means, well, you know,
if you get the data, we’ll look at it
and see then, you know?
So that’s kinda the best you can do.
It’s difficult to get certainty.
There’s definitely a lot of planning
around communication with FDA.
What do we wanna say?
I think of it a little bit
as kinda like going to the oracle in ancient Greece, right?
It’s sort of like, you know,
you have to plan and hope that, you know,
they’re gonna tell you.
You can interpret what sort of prophetic thing
they’re going to tell you.
Sorry, I don’t have a better answer for you than that.
Oh, but what I was saying earlier was there is something
called the Complex Innovative Design Program
where you can set up,
if they accept you, you get like two extra meetings
where you can review things like simulations. So if you wanna do something complicated, they’ll often say, ”Well, we wanna make sure type one error is controlled.”
And if the answer to that question is, "Well, we got a bunch of simulations to show you that it controls type one error,”
then you might wanna do something like that to kinda dig through the details of, well, how did you set up your simulations and all that.
Other questions?
I feel like I’ve been ignoring everybody over here. Got a question over here.
Oh, yes.
Thank you for the presentation.
The question is, is it possible to revise your SAP after the trial started? If the answer is yes, is there any restriction on it? So again, back to the blinded versus unblinded, right?
If it’s an unblinded study, you can, but it’s gonna be viewed suspiciously, for lack of a better word, right? It’s gonna be viewed as a post hoc change. Why are you changing this?
You suspected that something, if it’s a blinded study, yes, you can. You can amend your SAP. That’s not terribly uncommon. For example, you might, during the course of the study, still blinded, you might learn new information, new published data may come out. You might learn something about the baseline data on your study, you know, the distribution or something like that. So as a result, you may wanna pivot what your SAP is and if it’s still blinded, generally speaking, you could still do that and it’d be used pre-specified. Thank you. Yes. I’m very sure that there should be many variables to consider when it comes to this study. And in case of these small sample size studies, I’m pretty sure that a stratification might really be inefficient to contain all these variables at one place. And I’m very curious, how do you actually like manage when it comes to the small sample size? Yeah.
Yeah, also good question. Again, I think this is a good area for more research.

We had a group look at some simulations. Here's my qualitative assessment of what we found.

One, I think in general, people worry a bit too much about what you're saying. As long as like the marginals work out pretty well,

then you're actually probably still okay as far as stratification goes.

I think there's a bigger danger of bad luck imbalance.

I don't wanna speculate too much, but there was a competitor that had a study come out,

rare disease, small study,

just by bad luck, they had some imbalance in one other strata.

And maybe it could be the reason why the study, statistically speaking, failed.

And so, yeah, here's my sports analogy, okay?

So small studies are kind of like a football game where you're losing at the end of the game.

You wanna throw the ball 'cause you need to score, right?

The defense is going to be playing for that.

They're gonna make it harder for you to do that,

but you need to do it anyhow, right?
That's kinda like the way stratification is. Yes, it’s harder to do it in a small study, but you need to think about it and try to do it anyhow. 'Cause if you just throw your hands up and say, "Eh, whatever," then you might have what happened to you, what happened to this competitor.

And so we actually wrote a program so you could simulate. Hey, from my study, I’ve got X patients, these are the stratification factors. What’s gonna happen to my type one and type two error?" But you are right that in principle, you can’t overdo it. I just think the point where you overdo it is further out than most people think.

Two more minutes. Any other questions? Sorry if I’ve ignored online.

We have. I have a question. I don’t know how many people we have online. Let me just move to see if there’s the chat. Do I? To pop up. Oh, it would pop up? Okay.
That’s doesn’t look like we have any chat.

Can I ask a question?

So you mentioned time management obviously.

Can you tell us about sort of what is the work cycle of a biostatistician?

So are they working on many studies at one time?

Are they getting a lot of experience doing phase one or what’s the volume of which they’re working on and how?

Yeah, it’s, as you expect it, you know, it depends.

I mean what sort of study someone has assigned to you is a little bit random.

I mean what they need somebody to do.

It’s not uncommon for people to be assigned to say two to five studies depending on how big they are,

how short you are on people, et cetera, you know?

And so you have to try and manage that kind of work.

I was just talking about across those, you know,

say two to five studies.

You also spend, I’d say roughly 10 to 20% of your time doing non-project stuff.

Things I mentioned like the working groups, maybe some independent research,
maybe other kinda service to the department.
I mean, you know, obviously,
I spend time interviewing people, stuff like that.
So that’s kind of the breakdown of what people are doing.
And are they working in teams?
And you would have, you know, again,
you have a project level, right?
So you would have a project statistician,
somebody who’s somewhat more senior,
who manages the whole project.
And then under that person, you might have whatever,
you know, two, three, four,
depends how big the project is,
statistics who manage individual studies,
So you might have, you know, I don’t know,
10 studies in the project, right?
And you might have three statisticians
who each have three each or something like that
reporting to that project statistician
who’s kinda doing the overall work on the drug.
All right.
So thanks so much.
In the interest of time,
we’re going to go ahead and stop here.
But let’s thank our speaker again.

Great insight into the industry and have a wonderful day.

Sign in sheet.

Oh yeah.

We have a sign in sheet.

Thank you.

So we got a couple of ‘em up here.

You still need to sign in, please do.

The thing is that

well, technically, have like four, five.

(students chattering indistinctly)