Adrian Hernande...: 00:04 Hey, this is Adrian Hernandez, and welcome to the NIH Col laboratory Grand Rounds Podcast. We're here to give you some extra time with our speaker and ask them the tough and interesting questions you want to hear most. If you haven't already, we hope you'll watch the full Grand Rounds webinar recording to learn more. All of our Grand Rounds content can be found at rethinkingclinicaltrials.org. Thanks for joining.

Hi, I'm Adrian Hernandez, I'm the moderator for our Col laboratory Grand Rounds. Today, we're here with David Boulware, who will be reflecting on a recent Grand Rounds presentation entitled Lessons From Virtual Trials in a Time of Pandemic, the Minnesota Hydroxychloroquine experience. David, thanks for joining us and doing this.

David Boulware: 00:48 Happy to be here, Adrian. Thank you for the invitation.

Adrian Hernande...: 00:51 Well David, it was just terrific to hear what you all did to address the pandemic. Can you take us back in time a bit and reconstruct the events that led you to developing these suite of trials around Hydroxychloroquine?

David Boulware: 01:11 Yeah. I was actually at an NIH study section in DC, sort of in the beginning of March. I'd emailed someone at NIAID, and this was on Sunday, March 8th. I was flying back to Minnesota. Emailed to ask, "Hey, is NIH doing anything with outpatient trials as far as early treatment, or post-exposure prophylaxis?" At the time, they were trying to get up the adaptive design Remdesivir trial. They said, "No, they're focused on the hospitalized patients." CROI HIV conference had been canceled and was a virtual conference. So my team was supposed to be in Boston for the CROI meeting from that Monday through Thursday. I was sitting in the airport and I was thinking, we should do something about this.

So we flew back, and I emailed people that night. My team members said, "Hey, let's meet at 9:00 and we're going to do something about COVID." I wasn't totally sure what I wanted to do, but I knew that Hydroxychloroquine had some invitro activity against SARS, and it's available, it's cheap, it's off-patent. Basically, that Monday morning, I gathered my team together. Which normally does a bunch of Streptococcal Meningitis research in Africa, but they were all supposed to be at CROI and they all had free time, in essence, because their schedules were blocked off.

We started with a post-exposure prophylaxis trial.

Adrian Hernande...: 02:47 You had some prior experience dealing with pandemics. How did that influence what you did here?

David Boulware: 02:54 Yeah, I've worked in Africa for about 15 years now. I helped out with the Ebola trial in West Africa back in, gosh, 2015. With that, I didn't do a whole lot, but I went to Liberia. At the time, I was supposed to be there for two weeks but I was there for a week, and nothing was going on. But they were sort of in the process of still getting the trial up and running. They had a US protocol that was written, and I basically just spent the week mostly just rewriting the protocols that could actually be implemented in Africa, and writing consent forms, and doing a bunch of work on that Ebola trial.

I didn't actually do a whole lot, but I did some. I helped write the protocol, which was a big chunk, and write the consent form. I had kind of helped out before, so I had some connections with the NIAID staff and others, who I knew, that's why I could ask some of them a little bit.

Adrian Hernande...: 03:51 Were there lessons from watching what had happened or transpired around Ebola and delays in trials and issues around that that influenced what you did here?

David Boulware: 04:03 Yeah. I think the classic, which the 2015 Ebola showed is that by the time the research community gets organized and gets funding and gets stuff on the ground and gets stuff ready to go, boom, the outbreak's almost over. That was the case for the trial, we enrolled our first patient and it was like, gosh, was it early March of 2015, towards the very end of the epidemic. They were able to enroll enough patients to get some answers. It took five, six months to get the trial up and running. I sort of knew that, if you go through the traditional routes of let's write our grant proposal and try to get funding, that that was just not going to work.

Clearly, early in March when there was community spread happening, it was very apparent. I think that most infectious disease docs and most just physicians who were paying attention were like, this is going to get bad quickly, which is exactly what happened. Once there was community spread happening it was just like, this is terrible. Because I was kind of ignoring it in January, and February, it was happening in Asia, and it was sort of far off. But by the time the community spread was happening it was like, this is bad.

And you kind of stand around like, gosh someone should do something about this. And then you realize, well, maybe that should be me. That should be us. That was the attitude that we took. That yeah, someone should do something about this. NIH and BARDA and the federal government were clearly not really focused on outpatient management. If you think about, how are you going to change the epidemic, it's either by post-exposure prophylaxis, or early treatment to prevent hospitalization. Because the problem is not, the people with mild illness that get a little bit sick and recover, that's not a problem. But the people that get hospitalized.

In New York City, clearly, in early March, the hospitals were getting overwhelmed. If you just sort of break down the healthcare system, and people are overwhelming the hospitals, that's a problem. That's what we tried to focus on. There's lots of people working on lots of things. But most of the trials really were focused on inpatient hospitalized treatment. We thought boom, we should do a trial, and we're going to run it. At the time, I had a little bit of money salted away from various whatever talks I'd given or per diems for this and that, so I had a little bit of research funds put away.

So it's like, we're going to run the trial. We didn't have much money, but we're going to do it. How can you do a high quality trial that gets you a clinical answer, but yet also when you don't have a lot of money to do it?

Adrian Hernande...: 06:46 Right. Maybe talk a little bit about the so-called engineering requirements. It sounded like from the Ebola experience, you knew the traditional systems wouldn't work. That it wouldn't address the pandemic when it needed to. Then there's research limitations. What were the guiding principles you had, and you and your team, in developing this?

David Boulware: 07:11 Yeah. We're really familiar with FDA IND trials, and we do trials for cryptococcal meningitis, and TB meningitis now. We're very familiar with the traditional clinical trial model. Even when we're working in Africa, and the resource there, the paperwork and the documentation is very similar. In this case, we weren't going for FDA approval. It's already an existing medicine. The question is really, does it work? We decided to really design sort of a patient reported outcome would be, I think, the technical term for this. The patient reported outcome measure. For post-exposure prophylaxis, it's fairly simple because it's really, you take a healthy person that has no symptoms. The question is, do they get sick? If they get sick, what symptoms do they have?

It's a pretty obvious endpoint. You say, well, they can get sick of other causes. But you know, you live in the real world. The final question is, does it decrease illness and does it decrease disease? At the time, we thought that people would actually have access to testing. This is back in early March and testing was really problematic, as everyone remembers, but it was expanding. We thought well, this has got to get better, but it really didn't for quite a while, unfortunately.

Fundamentally, if people get sick and do they have symptoms? Do they have headache? Do you have cough? Do you have fever? People can say it like that. Especially if you start healthy. That's kind of how we designed it, first the post-exposure prophylaxis trial. Focused on that. Because it's like, this is something people can report. There were a lot of healthcare workers that we reported. So if a healthcare worker who starts out healthy can tell you if they have a cough or not. It's not terribly complicated. Obviously if you have lab testing, that's great. We would've liked to do more lab testing.

But at the same time, the perfect can't be the enemy of the good.

Adrian Hernande...: 09:08 Right. No I guess that's very true. How did things go? What was it like, getting things started up?

David Boulware: 09:18 Well it was nothing crazy. I've got about a dozen people that work with us, work with me. I shouldn't say me. We all work together. It's a really great team experience. We've worked on neglected diseases where it's us doing the clinical trials in Africa, there's no big pharmaceutical company that's sponsoring stuff, and a bunch of people do the work. It's like, you've got to do the work yourself. Having done a number of trials, I was familiar with what needs to get done, and so were most of my team members. We rapidly wrote a protocol, rapidly in less than 24 hours. And we used Google Drive and Google Docs, so you've got multiple people working on the same file at the same time to work through things fairly quickly.

You know, [inaudible 00:10:06] B, I've done FDA IND submissions before, so I filled out that paperwork and FexExed it off. We started, how are we going to collect the data in a base? So we started REDCap database and survey system, do that. We kind of worked through a lot of the regulatory processes and the logistical processes, talked to pharmacy, bought the medicine. That was probably one of the biggest stresses, is there enough medicine? When I first bought it, just

out of my own funds, I think it was 50 cents a pill or something like that. Then two days later, when I bought it, it was $1.50 a pill.

Adrian Hernande...: 09:18 Wow.

David Boulware: 10:44 It was rapidly increasing in price. Then rapidly, there was a shortage thereafter. But we at least had a supply for our trial. Yeah. It was a little bit crazy. But you know, in the span of eight days, we worked through all the things you needed to do to get a trial up and running.

Adrian Hernande...: 11:02 Well, you were able to do a number of studies in this space, I hear. What were key lessons learned?

David Boulware: 11:12 Well, one of the things, we ultimately did sort of ... I guess, we had three trials. The first lesson we learned was that we were excluding people from our post-exposure prophylaxis trial because they were sick. They were already symptomatic. By the time they got the medicine, or by the time that they filled out the survey. So we rapidly pivoted and expanded to an early treatment trial as well. It was sort of both post-exposure prophylaxis and/or early treatment. That, we had a good idea on. That started just a few days later. The issue of diagnostics was still a problem.

I think that's still a problem, that just for an early treatment trial, or post-exposure prophylaxis, you probably need to get the medicine to people as soon as possible to alter the disease course. Because if you give people some sort of medicine a week into the disease course, probably their course is already set. So trying to get things as quickly as possible, we took some sacrifices and for our early treatment trial, we enrolled people either who had a PCR positive diagnosis, which was great.

Or if they had a contact who was PCR positive. If your spouse, or someone you live with in your household or your work was PCR positive and that was your exposer. And you didn't have a test, or your test was pending, we took those people as well. That was a good idea, because still today, the turnaround time for testing is two or three days in a good situation, sometimes even longer. I had a friend of mine actually recently, I won't say the state, but I referred them to ... Was it the Act Two or Act Three? I forget what the number system is now.

But basically one of these outpatient treatment trials for monoclonal antibody. And her spouse was sick, and she had two

or three kids of hers were sick, and they had positive tests. She wasn't sick yet. I was like, well, you should enroll in this trial because monoclonal antibodies probably work, and they probably work early. If you get sick, you should totally do it. I told her the day before she got sick, here's the contact, you've got the consent form stuff. Something like the next day, predictably, she got sick, unfortunately.

But they don't actually do the tests, their turnaround testing was PCR, so it was a couple days. Go to XYZ commercial pharmacy chain and get a rapid test, which is a lateral flow assay. She was negative, because lateral flow assays aren't quite as good as PCRs, which people know. But they're reasonable. It was negative, so they couldn't enroll her. They were like, well ... That was on a Thursday, and time goes on. She's sick, and she can't get out of bed. Can't get repeat tested. Then it was like the next Monday, she goes back to get a test. It's like, now she's almost out of the enrollment time period to get a PCR.

Ultimately, this person who was told, you should enroll in this trial a day before they got sick, ultimately couldn't meet the enrollment criteria just based on the test turnaround time. This is in November. To do an early treatment trial is really hard. I think one of the lessons for other trials, and for the FDA potentially as well, that you have to have some realism in life of your enrollment criteria. Because you could have perfect enrollment criteria, but then not be able to enroll anyone. Particularly for outpatient trials.

For hospitalized trials, you can get test turnaround really quick, usually for most facilities, and they're coming to you. But for outpatient trials, it was a little harder. We use the accepting logic linkage of either PCR testing themselves or people who had a household member or known exposure to a PCR positive person and had compatible symptoms. That was something we did, people have criticized us. It's like, not everyone was PCR positive. But you know, we did analyze this on the back end of A priority, this is a subgroup analysis, if you're PCR positive, or if you're contact PCR positive, you're enrolled on a pending test. Those were subgroups that we had predefined for analysis.

That was kind of how we did it. I think that's one real lesson for people doing outpatient trials, that if you're wanting only PCR positive people, which that's a nice, very clean, perfect world scenario. But if it takes two or three days for them to be symptomatic before they get tested, and the test turnaround time is two or three days, rapidly people are going to be six,

seven days before they enroll in any early, early treatment trial. Which is no longer early. Whatever intervention probably is not going to work if it's a week into their illness.

That, I think, is one large lesson, perhaps. But I'm not sure if that's what you're looking for.

Adrian Hernande...: 16:04 Yeah. You know what? It certainly sounds like the trials have to meet the context, or so-called the real world. As you noted on the outpatient setting, it's very different than, say, an inpatient setting where there's anything available at any time, any time of day. Final question for you as we close up, obviously we're still dealing with the pandemic. What are things that need to be done over the coming weeks and months here for the pandemic in terms of clinical trials?

David Boulware: 16:39 Well I mean, there's many things about the pandemic. But I think, we're now, what? Eight months into the US pandemic. The only medicine that has a survival benefit is steroids. Which is like, that's it? Really? If you think about it, okay, there's the monoclonal antibodies that we think probably do decrease hospitalization if they're given early to serum negative people. But if you look at what the actual data is, we haven't done a lot, I guess I would say. Remdesivir is kind of like a little plus minus, and that's a whole conversation in itself. But steroid's basically the only thing that's been shown to have a pretty clear survival benefit.

That's rather disappointing, I guess. I think there need to be more clinical trials. That who's going to fund that? You would think the US government would be interested in that, but if people want the perfect gold standard, ideal, say it's going to cost $50 million, that might not always happen. I would say there needs to be more innovation. A lot of the clinical trials have been completed. We did one post-exposure prophylaxis trial that we had privately funded, and there's been a second one in the US completed, and that's it.

Then for pre-exposure prophylaxis, we've done one. NIH, obviously, the Core Network is doing one. But there's a lot of different other medicines. There could be other trials being done. I would say that there clearly is plenty of patients with COVID. The ability, there's certainly a need. But also, there's just leadership that needs to happen of people, like American citizens, need to sort of be wanting to be altruistic to volunteer for research studies. I think that concept of altruism for overall societal good has not been something that's been really

communicated very well by leadership. Because that's really beyond even the scientific community.

That people really need to help the overall cause. For all these trials, some of them don't work, but very few are harmful. We still need, unfortunately we need people to volunteer for research studies and randomized clinical trials to really help generate high quality data. That starts with physicians to refer patients. It starts with just the attitude in society for science and really wanting to help contribute to the overall societal good. Even if you may not, yourself, have benefit. That speaks really to altruism, which is really, I think, key for clinical research.

Adrian Hernande...: 19:27 That's great, and I certainly agree with all this. Extraordinary times take extraordinary efforts. And to think differently. We all have to lean in. David, thanks for joining us on this podcast to share your views and lessons around virtual trials in a time of pandemic. For the rest of you, please join us. Thanks for joining us this time, and join us for our next podcast as we continue to highlight fascinating and informative changes in the research world.

Thanks for joining today's NIH Col laboratory Grand Rounds Podcast. Let us know what you think by rating this interview on our website, and we hope to see you again on our next Grand Rounds, Fridays at 1:00pm eastern time.