Adrian Hernande...:	00:04	Hey, this is Adrian Hernandez and welcome to the NIH Collaboratory Grand Rounds Podcast. We're here to give you some extra time with our speaker and ask him 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.
Lesley:	00:28	Today we're here with Robert Califf, who will be reflecting on the keynote address that he gave for the recent NIH Collaboratory Workshop entitled Advances at the Intersection of Digital Health, Electronic Health Records and Pragmatic Clinical Trials. Rob, welcome to the Collaboratory podcast. Great to have you with us.
Robert Califf:	00:52	Thanks, Lesley. Good to be here.
Lesley:	00:54	So you posed a question in your talk that was, can the COVID-19 crisis actually lead to reformation of evidence generation and of that entire ecosystem? Can you refresh us as to where we were heading into this crisis?
Robert Califf:	01:16	Well, as you well know having just finished a term leading the DCRI, our evidence generation system had a lot of problems before we came into the crisis. Of course, everything should be related to history and there's no doubt that we've learned a lot about how to do the right studies, generate the evidence and disseminate it.
Robert Califf:	01:42	But we were facing a situation already where the amount of new technology and the complexity of all technology was far outstripping our ability to do the right studies to generate the evidence we needed. And not only were we facing a situation where for example, less than 10% of major guideline-based decisions in cardiology were not based on high quality evidence. But we were also dealing with an escalation of costs that was making it impossible, even if we knew the right things to do and had willing people using the methods that were currently in place. And the systems that were in place for everything ranging from regulation to payment, to how the studies were done.
Robert Califf:	02:31	There was just no way we were going to be able to keep up and provide patients or clinicians with the evidence they needed to make good decisions. So we were already facing a bit of a crisis before the new crisis hit.

Lesley: 02:48 Yeah, that's true. So you described almost a fork in the road that we face now that we are in the middle of this pandemic. Talk a little bit, if you will, about what the paths are that we can go down as a result of this. What are those options?

Robert Califf: 03:08 Well, it's always useful I think to simplify when we talk about choices. Realizing that in reality, there is a huge middle ground and many options along the way. But basically when COVID-19 hit, people responded magnificently. And so everyone from investigators to patient volunteers, to administrators, lawyers, everyone pitched in. And almost every role was put in advance with the general [dictum 00:03:46] that common sense should prevail given the fact that we were facing the most serious health threat of our lifetimes. And now we saw how many studies you could get started in a remarkably short time. Many of them very well designed and taking advantage particularly of digital technologies that are not new.

Robert Califf: 04:11 We've talked about them for a while, but there are many reasons why they just weren't being adopted at the rate they could have been. And so we're going to be at a fork in the road as we get more into the chronic phase of the pandemic. I wish I could say after the pandemic, but I don't think the models are showing that we're going to be out of this for a while, but as we move into more, the chronic phase. We can either go back to the way it was, or we can take advantage of what we've learned along the way, and perhaps really rev up the system, not just for COVID-19, but for all the other needs that people have for answers to questions to guide their healthcare decisions.

Lesley: 04:53 Rob you mentioned several aspects of clinical research that have really accelerated over the last few months. Maybe we can touch on some of those individually, what have you seen from a regulatory context? And how has that changed? Do you have a unique perspective given the time you spent as commissioner of FDA?

Robert Califf: 05:22 I think the FDA responded magnificently on the research side of the equation and put out a set of guidances that instructed the community that something called the COVID flag could be used, which many of us have come to like quite a bit. And the idea here is that business as usual was not going to work. It didn't matter whether you were starting up a new study related to COVID or you had a new study planned in some other disease, or you had an ongoing trial in another disease. You simply couldn't see people back for the usual study visits and for the

COVID related trials, there was not just an urgency, but really an emergency.

Robert Califf: 06:08 And so the idea is, think through what you need to do using quality by design. Get rid of all the things that would either make it impossible to do the research, or would delay COVID related research. But using quality by design, stick to the principles that lead to good evidence generation and then keep records of why he made the decisions that you made so they're available when the dust settles and everything can be put back together.

Robert Califf: 06:44 So I think in that sense, I think we've learned that we can design more efficient studies that can start more rapidly and can focus on the outcomes that matter. There's also going to be a whole new area of analysis related to competing [inaudible 00:07:05] because in many cases, the outcomes or endpoints that were planned, can't be measured the way they had planned. The example that I thought was most striking to me was in pulmonary fibrosis where patients literally can't get near a clinic because any COVID infection would be lethal. Most likely the patient community and the research community got together and figured out how to measure things at home that matter. But regulation is not just a matter of FDA. There are many other regulators in the system, including all of our local institutions. And it has been remarkable how many institutional bureaucracies have responded very well to move things along to get studies underway and to oversee them.

Lesley: 07:57 You noted to the necessary rise in the use of digital technologies so that we can actually continue research during this period. What have you seen that gives you maybe hope about how quickly we can answer key questions?

Robert Califf: 08:21 Oh, there's a great parallel here between the clinical world and the research world. It is not exactly a great revelation that digital technology would enable a visit to occur without being there in person. And actually, I guess a third analogy is our families with mother's day yesterday. I think many of us had coast to coast Zoom broadcasts or whatever technology was being used to bring families together. And while it's not exactly the same as an in person visit, there actually a number of advantages that began to come out that you can really see. For example, I think in all three situations if we talk about clinical research and personal life, I think people are actually contacting each other more often. In the clinical world, for example in

addiction program that I'm involved in, the number of times people miss visits has precipitously dropped.

Robert Califf: 09:27 In other words, if all it takes is a phone call with a visual, with a phone call, people rarely miss their visits. Whereas if they have to get in the car and drive to the clinic, there's a much higher chance they're going to miss it. For chronic disease, you can follow people for shorter individual visits, but you can have many more to follow their trajectory. And I think many clinical trials have been designed that way so that the followup and visits that would have been scheduled in person at greater expense and a lot of headache getting back and forth to a clinic can now be done virtually.

Robert Califf: 10:14 I'd also add, one area that has really been amazing to watch is consent in situations of sick patients with COVID, even inside the hospital. Virtual consent is being obtained to reduce exposure or personnel to really sick people for some of the very important research being done for people who are critically ill with COVID. So I think we now have the groundwork for what we all knew was possible and it was just being held up either because of the way things were paid for or the interpretation of regulation. And I think we can look forward to a much more efficient hybrid system.

Lesley: 11:04 Electronic health records has been a topic of discussion, certainly between the two of us for several years now. What have you seen in terms of data access, health record access, over the last several months that again gives you either encouragement or makes you feel slightly discouraged?

Robert Califf: 11:30 I think the willingness to use electronic health records for research data is obviously much more pressing and so people are willing to do it. And I might turn the table a little bit on you Lesley here since you're the expert on this, but it keeps reminding me that while we have figured out how to curate EHR as the common data models and a manual process. We still don't really have a fluid system of sharing the data and automating this so it's just ready to go, like it really should be. You would think with the amount of money that we spent on electronic health records and people's willingness to share their information, particularly in this situation that at some point, it would never be as simple as just pressing a button, but it ought to be easier yet than it is.

Robert Califf: 12:30 I will note that I was just looking this morning at a report from the UK of a symptom tracker in 2.3 million people. Gives you a

pretty good power to look at the symptoms that were predicting a COVID infection. And when we think about a country like the US with 300 million people all with electronic health records, I guess almost 350 million now. There's really almost no question you can think of where there wouldn't be adequate power to answer the question, if we can just get these records organized and curated. So I want to turn the tables on you a little bit here, Lesley. How do you see this?

Lesley: 13:17 You've identified exactly what the problem is and I see the same problem. The solution really I think requires us all to think differently about how we bring data together in near real time ways. The approach of building it block by block by block and curating as we go, that takes a lot of time. And a lot of time that feels like right now, we don't have. So I spend some of my time thinking about how we can come at this from a completely different angle. I haven't come up with the answer yet, but I'm pretty sure that the old way of doing it again, where we secure data and permissions and link data on a case by case basis. That is just not working at all. So maybe we better come back in a few months and see if I've come up with anything better than that.

Robert Califf: 14:31 Now that you have all this spare time with Dr. Hernandez taking over the DCRI, I think this would be a great place for you to spend your time. And obviously with my work now at Alphabet, it seems to me that part of the solution has to be the use of automated algorithms with machine learning, to not get you 100% of the way there, but to take away so much of the human labor and focus the human labor on the places where it really makes a difference. And there'll be plenty of those because human interpretation, I think is still going to be important, a fundamental underlying issue that I'm thinking a lot about now, even since the Grand Rounds, is this really complicated trade off of our beliefs about the ethics of all this.

Robert Califf: 15:25 What is the right to privacy versus the right to health that is improved when information is shared? And this is not a question for me working for a tech company to answer. Now, this is a question for people and universities and other parts of society to answer. But I do think the crisis has really called this issue into the forefront of people's thinking.

Lesley: 15:55 Yeah, I agree. I agree. So Robert it's always just a real treat to talk with you. Today's been no exception to that. As we wrap up, what do you see as maybe the most important thing or few things that those of us who work in this ecosystem can do to

		make sure that the progress that we've made in some areas not just continues, but accelerates over time.
Robert Califf:	16:28	I really hope we'll look carefully at what we've learned from this experience and take the things that worked and insist that they be continued with a focus on generating high quality evidence at the lowest cost in the fastest way possible. That's what all of us would want for the medical problems that we're concerned about. We'd like to know the best thing to do, whether it's a use of a treatment or a better diagnostic test, or even implementation of health services in a particular way. And so I think as we go through the crisis and we're certainly not out of it yet, keeping records of what we've done and then reflecting and implementing, going forward.
Robert Califf:	17:18	I do believe that the regulators, for example, will be very interested in doing that because so much has been learned. And I hope the academic medical centers will really take out the mantel and ally with the patient groups to bring forward the things that work during this crisis.
Lesley:	17:39	Great. Well, thanks again for a great conversation Rob. It's been a really good to have you join us on our podcast series and for those who've tuned in today, I invite you to join us for our next podcast as we continue to highlight fascinating and informative changes in the [FirstSearch 00:17:58] world. Thanks again, Rob.
Robert Califf:	17:59	You bet I really enjoy these Grand Rounds and look forward to listening to the future speakers. Take care.
Adrian Hernande...:	18:10	Thanks for joining today's NIH Collaboratory 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 1:00 PM Eastern time.