Scientific Advancements in Gene Therapies: Opportunities for Global Regulatory Convergence
Hybrid Public Workshop
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Morning Transcript

Welcome
Susan C. Winckler, RPh, Esq., Reagan-Udall Foundation for the FDA

Susan Winckler:

All right. It's time to kick off our meeting. Hello and welcome to those of you who are here in the room and those who are joining us virtually. My name is Susan Winckler, and I am the Chief Executive Officer at the Reagan Udall Foundation for the FDA. We are so pleased to be partnering with FDA and with the Bill and Melinda Gates Foundation to host this important workshop on scientific advancements in gene therapies, opportunities for global regulatory convergence. So I have just a few housekeeping issues that we need to run through so that we can have a productive day. So I'll remind you or point out that most of our speakers, and those of you who are in the room, are here at our foundation headquarters.

We also have a significant number of virtual participants. Because of the size of the meeting, virtual attendee cameras and microphones will remain off through the event, but you can engage through the zoom Q&A function. For those of you who are in the room, we'll take your engagement through some index cards that, if they weren't available at the registration table, are being gathered right now to provide to you so that you can write down questions, and I will do my best to address those questions as we have time in the session. So our primary engagement will be through the stage here. We do want to hear from you. So a reminder, please use the Zoom Q&A function if you are remote, and if you are in person, use the index cards. I will also say, if you are here in person, please don't log into the zoom.

It is not good technologically, nor for the engagement that we'd like to have with each of you. I will note we are recording the meeting, and we will post the recording in a transcript to our website, reaganudall.org, later this week or early next. So before we dive into the agenda for the day, I, again, want to thank our collaborators at the Bill and Melinda Gates Foundation and at FDA's Center for Biologics evaluation and research. The partnership in constructing this meeting has just been extraordinary, and we are excited for the time that we are going to spend together, so a reminder of our agenda. We will first invest time in learning about the current state of gene therapy, and then talk through in the availability or acceptance thereof in low and middle income countries.

Then, we'll turn this afternoon to talk about the next generation of gene therapies and what's in development, and have a collaborative discussion with regulators and many others to say, "What is it that we might need to do to take advantage of that new technology?" So we are ready here. The full agenda is available on our website, and you should have received one when you checked in. It is time for me to get out of the way and start with our opening remarks. I will turn first to Dr. Peter Marks, who serves as director at FDA's Center for Biologics evaluation and research. If you note that he's not here on

stage yet, he will be later today. He's joining us virtually for his first opening remarks, and then he will be here in the room later. So Dr. Marks, are you ready to pick up the virtual mic? I see you. Take it away, sir.

Opening Remarks

Peter Marks, MD, PhD, Center for Biologics Evaluation and Research, FDA
Julie Makani, MD, PhD, Muhimbili University of Health and Allied Sciences (Tanzania), Tanzania High Commission to the UK
Mike McCune, MD, PhD, Bill & Melinda Gates Foundation

Dr. Peter Marks:

Okay. Thanks very much. First of all, thanks so much to Susan and to Reagan Udall Foundation for making all of this possible. Also, thanks to the Gates Foundation for engaging. This is, I think, for me, a very important topic. When I reflect back to the promise of gene therapy, I see how much of a difference it is starting to make here in the United States. We finally come over our hurdle in some ways, first, with the cell-based gene therapies, and now with the directly administered gene therapies, and on the horizon, we have incredible growth potential, as you'll hear about this afternoon, from the developments in genome editing with CRISPR and what may be possible in the future.

But when I step back a moment, it would be such a shame if we only see these advances come to high-income countries, because gene therapy, in many ways, is so important for low and middle-income countries. Why would I say that? It's because when you step back and think about it, for any number of diseases in high-income countries, we are able to provide a level of supportive care that keeps people alive for long periods of time. An example of that, if you want a specific one, is for beta thalassemia major, where with chronic transfusion therapy, iron chelation therapy, and good monitoring of iron levels using MRI, one can live a relatively normal life today with beta thalassemia major, and something that was not possible years ago, we see women who can bear children, because they're not iron overloaded and they're adequately controlled.

But in a low-income setting where that supportive care is not available, in the absence of gene therapy and affordable gene therapy, there's not going to be a solution. So I think this discussion today that we're having of, how do we get to a place of having the right regulatory environments in place and having gene therapies progress to the point that the cost and our manufacturing abilities get to a place that we can make them available widely, this will be, I think, a really important discussion to have moving forward, so really look forward to the discussion today. I think this is a departure point for conversations that will be ongoing in the future. Some of them have already started, obviously, but really excited about moving forward, and thanks again to Reagan Udall.

Susan Winckler:

Great. Thank you so much, Dr. Marks, and we look forward to seeing you here in person later today. Second, in our opening remarks, I want to welcome Dr. Julie Makani to the podium. Dr. Makani serves as the principal investigator of the Sickle Cell Program at the Muhimbili University of Health and Allied Sciences, Tanzania, and science advisor at the Tanzania High Commission to the UK. Dr. Makani, I'll welcome you up here.

Dr. Julie Makani:

Thank you. Thank you very much to the Regan Udall Foundation for inviting us, and thank you to the Gates Foundation for letting us share our perspective. So I was asked to make some remarks from the perspective of patients and providers, both medical doctor and scientists, and I also have family

members and work with a lot of patients who have sickle cell disease, which is one of the most common genetic disorders in the world. But what I'll do is I will expand a little bit in this opening remarks to talk about more than just the patient and the providers. I think we have researchers here, which is, and you will hear a lot about the gene therapy in the next couple of hours, and then policymakers, particularly in terms of regulators.

I think when we talk about perspectives, we really need to put patients at the heart of this discussion, and we'll have, during the panel discussion in the second session, we will have the perspective from patients. Why do I say this is important? It's because, as scientists, as policymakers, as providers, we tend to think about the health system. We tend to think about the complexities, and we really need to focus and make sure that we focus really and prioritize patients. We spent a lot of time in Tanzania and with colleagues in other African countries, thinking about what we need to do, and came up with a very, very systematic approach to say, "This is how we'll approach providing healthcare and finding a cure for sickle cell disease." What we found disrupted this completely, in addition to the scientific advances that you hear about, was what the patient wanted. Patients came up to us and said, "When can we get access to cure? How can we get access to it?"

The reality is that if you do not provide it, as a provider, patients will find a way of getting the medicine, and that's why regulatory authorities are important. That's why providers are important, to listen to what the patients are asking for. The second thing is I really wanted to talk about access. When we talk about access, a big part of it, and this is what Peter said at the beginning, is really focusing on the majority of patients. For instance, with sickle cell disease, 80% live in Africa and in India, is that when we talk about access, it is beyond low and middle income countries. You look at the disparities of access to medicine in the US here, in the UK, the problems are the same, and therefore, rather than look at it from the perspective of what's happening there and what's happening here, let's work together and see how we can learn from each other, because there are some ways. There's a bit of an echo. Is that just me?

Dr. Peter Marks:

You're good?

Dr. Julie Makani:

Yeah? There is a lot that we can learn from each other when it comes to global, specific regions of specific countries, because there are a lot of similarities and differences. One of the things, working with Mike McEwen as part of the Global Gene Therapy Initiative, one of the things that we spend a lot of time doing is trying to get people not to see the differences, but to see the areas of convergence. I hope that, as part of this discussion today, we'll be able to look at where we are similar, where we can converge, and where we can link together to learn from each other. I think my final comment is really from the perspective of this tendency of dichotomizing discussions. There's a real tendency, for various reasons, completely valid, of saying it's, "either or." These things are mutually exclusive. You cannot talk about gene therapy and curative therapy when you haven't even sorted out comprehensive care, diagnostic newborn screening, or in the case of sickle cell, newborn screening or access to hydroxyurea.

In the same way, you have a tendency of saying, "Well, you cannot talk about patient care, where you're talking about medicines or interventions that are very expensive," when you have not even sorted out the basics. Now, I, for a long time, and I think this is why this is talking about convergence or when we talk about integration, is that we shouldn't look at it in an either/or. We shouldn't look at it as a mutually exclusive approach. We need lots of people working together, finding solutions that can address this problem, because it's too big to be dealt with in one way, and so by approaching it in an integrated

manner, in a manner that where we converge, we hope that we can address this issue and make sure that access to medicine is not just limited to a few people, and it's available to everyone. So thank you very much for listening, and I hope that the rest of the day will be very, very informative and a learning opportunity for all of us. Thank you.

Susan Winckler:

Great. Thank you so much, Dr. Makani, and what important words that I know will resonate throughout the day. Dr. McEwen, you can go to the podium because I'm almost to you, but words that are going to resonate throughout the day, about assuring that we are patient-centric and thinking broadly about all of the components that are important in this space and integration, so I expect some of those words we are going to hear again and again. So our final opening remarks come from Dr. Mike McEwen, who serves as head of the HIV Frontiers program at the Bill and Melinda Gates Foundation, and a Professor Emeritus of Medicine at the University of California San Francisco. Dr. McEwen, I'm going to step out of the way and let you pick it up.

Dr. Mike McCune:

Thank you, Susan. It's been great, I should say first off, for my team and your team to be working together on this meeting, so thanks for all your work on that, and greetings to all of you. Good morning and good afternoon or good evening, wherever you are in the world. I am at the Gates Foundation. The foundation was set up 20 years ago with a motto that every life has equal value in order to bring life-saving care for people around the world, mostly with infectious diseases. HIV, TB, malaria. I came there six years ago after 40 years of working in San Francisco at a public hospital with patients that had HIV disease, taking care of them and doing research. I'm gratified to say that we made a lot of progress during that time.

If you've got HIV disease now and you live in different certain parts of the world, you can gain care, you can get access to antiretroviral medication, and if you can take those antiretroviral medications every day, you're good to go, and there'll be better therapies coming that will presumably be even less often that have to be taken; however, in low and middle income countries, and in resource limited parts of our world in the Bay Area too, things are not so good. It's hard to get care. It's hard to afford the medications. Even getting the medications is sometime associated with stigma. Taking them on a daily basis is really hard, so even after 40 years of wonderful research, we can diagnose the disease, we can treat the disease, but we cannot get the therapies to the people that need the therapies, and that's a problem.

600,000 people a year die still of HIV disease. 1.3 million are infected, newly, every year. Those numbers are not changing. They're not exactly flatlined, but they're not going down. At the foundation, an effort was started about six years ago to ask the question, "Can we have another approach?" One that would be safe, effective, affordable, accessible, acceptable, that would be given as a single shot that would allow for people to have durable, antiretroviral-free suppression of HIV disease to lead a healthy life, to prevent themselves from infecting others, to prevent themselves from being infected once again. That, we considered might be done by what we call in vivo gene therapy, where a shot in the arm could actually send a vector, a vehicle to target cells in the body.

In this case, it would be very rare hematopoietic stem cells, the mother cells that give rise to all the other cells infected by HIV and protect them from becoming infected with HIV. This is the topic of many talks that you'll hear about today. It's in contradistinction to ex vivo gene therapy, in which cells are taken out of the body and modified and put back in. But you'll hear all about this. It was a stretch, to say the least in the beginning, to imagine that this could happen. We didn't have a clue about how to target

the cells. In the case of HIV, we didn't have a clue about what to do once we got there. For sickle, though, we knew. We had decades of research, the research that led to the approvals, just last year, of two life-saving therapies for sickle taught us that what we could do in hematopoietic stem cells in vivo, if we could hit it, would be something that might confer benefit.

So we began to incentivize academicians, some of whom you'll hear about today, companies, some of whom you'll hear from today, to really push the boundaries of in vivo gene therapy and to ask the question, "Can this be done?" And the work has gone, as you would expect, with a lot of failures, but some notable successes and, at the end, much more quickly than we would've imagined. Hence, again, the reason for this meeting today. There will soon be, before you can say, "Boo. I mean, two to three years." That's fast, right? In our life. Therapies, coming to the clinic with the optimistic compression that some of them will be safe, and that some of those that are safe will be effective. We got work ahead of us, and that's really why we're here. If we can show safe and effective therapies in the clinic for sickle or for HIV, how do we make them accessible to everybody? For instance, might there be a global target product profile that everybody could agree upon, which would meet regulatory approval in one country that would blanket all the other countries?

This would be a huge step forward, really lowering the barriers for entry of innovative therapies into the market. Well, I should say into the clinic around the world. There's work to do after that, right? We have to figure out how to distribute it. We have to figure out how to pay for it. We have to figure out, importantly, how to make it acceptable and find it to be acceptable to the people that would get it, but that's the work that will go forward. I'll just end by saying, we'll focus on sickle today. We'll talk a little bit about HIV, mostly me. There are other diseases of public health importance, cardiovascular disease caused by hyperlipidemia, chronic viral infections that lead to that could also be approached by in vivo gene therapies. These two would be ones for which the pathway would be laid by the work that we started today, so thank you for joining this discussion. It's going to continue. Like Peter said, it's continuing already, but there'll be a lot of work to do in the future, and I thank you for starting it today.

Session 1: The Current State of Gene Therapy

David Williams, MD, Harvard Medical School
Eric KariKari-Boateng, MS, Food and Drugs Authority (Ghana)
Kwasi Nyarko, PhD, WHO Regional Office for Africa (WHO-AFRO)
Maneesha Inamdar, PhD, Institute for Stem Cell Science and Regenerative Medicine

Susan Winckler:

Great. Thank you so much, Dr. McEwen. So with that, we've kicked off with actually our three doctors, Marks, McConey, and McEwen. We did not mean for that much alliteration in one session, but we have delivered on it already. So let's turn to our first session of active learning. And so, to launch that, we are going to turn to Dr. David Williams, who serves as chief of the division of Hematology Oncology, and the Leland Fikes professor of Pediatrics at Harvard Medical School. Dr. Williams is going to describe the global landscape of gene therapy, the different types of gene therapy, and the post-marketing requirements and infrastructure needed for long-term monitoring. Dr. Williams, we gave you a lot to do in a short period of time.

Dr. David Williams:

Yes.

Susan Winckler:

But I know everyone is ready to listen.

Dr. David Williams:

Thank you.

Susan Winckler:

Please take it away.

Dr. David Williams:

Thank you. Thank you very much for inviting me, Susan, and I'm glad to be here. I have a couple of disclaimers. One is Mike told me you can't talk about your own research, so I can't talk about my own research, but he says, "You've got to talk broadly about the field and cover as much as you can," and I'm going to try to do that, but I have to say I'm not an expert about this stuff. There's many more informed people, some sitting right here in the audience," so take that with a grain of salt, if you will. Let me see here. So here are my disclosures. I think, since I'm not talking about my own work, I don't have to worry too much about that.

What I'm going to do is a quick overview of gene therapy, a quick overview of the FDA-approved products, two short vignettes, Mike already alluded to this, of success in sickle cell disease. I'll talk a little bit about at least my impressions of some of the impediments of gene therapy entry into low, middle income countries, which has already been said isn't just for those countries. It's in parts of our country also. Then, if there's time, and there may not be, a little bit about the institutional infrastructure that we built at Boston Children's Hospital, that's allowed us to do lots of clinical trials in this area, but also now be a center for the commercial products. So by way of a primer, a short primer, just to remind folks, there's essentially two broad areas of gene therapy. Already alluded to ex vivo gene therapy, where, as you can see, the cells are taken from the body taken to a GMP facility, had gene transfer occur usually by, in the past, a viral vector, now at other methods.

And in vivo gene therapy, where the transfer vector or vehicle of the genomic material is directly injected into tissue or usually the bloodstream, with the liver being often the target. These two broad methods both have real advantages, and depending upon the disease, one uses the platform that's best suited for the disease, but they also have challenges. And these, some of you know very well. Ex vivo is very complex. The cost of manufacturing the cells is quite high. There's a real risk, because it's integrated vectors into the genome of mutagenesis, and at least currently for most diseases, it requires a very long inpatient stay in an ICU type setting, because you basically need to make space in the bone marrow to accept the gene modified cells. Usually these are hematopoietic diseases or diseases that can be addressed with hematopoietic cells. On the in vivo side, there's been issues with the immunogenic response to capsid proteins of the viral vectors.

There is some question about the persistence of expression, because in general, these are not integrating type vectors. You have to deliver the genome to the tissues that you're trying to modify, and there is some risk of mutagenesis because there is rare integration that takes place even in non-integrating vector systems. So this is just the landscape, if you will, of ex vivo gene therapy. You can see here the cells are taken out of the body. Usually there's stem cells, hematopoietic stem cells that are mobilized with different agents. They're taken to the laboratory where gene transfer occurs, either with viral vectors or liposomes now, and after the cells are ready, then the patient is admitted to the hospital. They're given what's called myeloablative conditioning, and then the cells are infused and grafted. Myeloablative conditioning means basically chemotherapy or radiation that eliminates all the stem cells that are in the bone marrow.

And so, during a phase of about three to four weeks, that individual is completely dependent upon exogenous sources of red cells, white cells and platelets, basically, and they're very immunodeficient. In vivo gene therapy can be done in a number of ways. Probably the first and infamous of these is adenovirus. This was the method that was used that caused the death of the Jesse Gelsinger back at the UPenn, way back in 1999. More recently, adeno-associated virus vectors, which have a good safety profile, and have been shown in some instances to have long-term expression. You'll hear much more about this, this afternoon, and actually, most recently decorated or lipid nanoparticles that are non-viral, but carry the genome within the lipid nanoparticle itself, and that's been a real source of recent advances in the therapies in vivo. Now, in these, basically, the genetic modify modification occurs by just injecting intravenous, generally, your carrier payload.

So these are a list of the FDA approved gene therapy products, and I've broken them up by color into in vivo and ex vivo. They go from SMA, one of the first and luxturna, which is a retinal gene therapy to ex vivo, such as Adrenoleukodystrophy, skysona, transfusion dependent thalassemia, hemophilia, Duchenne's muscular dystrophy, and metachromatic leukodystrophy, so these are all now FDA approved. Actually, at our institution, if you can believe it, we've already treated over 100 children with commercial products for gene therapy, so it's a very fast evolving area. There's also, of course, CAR T cells that have significantly affected, particularly B-cell leukemias and outcomes. That's the most successful of these, not as successful yet in solid tumors or even in myeloid leukemias, but these are a list of those products, and have changed the face of in-stage relapse leukemia, and now using up front in some places, actually.

Then, on the pipelines, there's several, but here's a couple. LAD is one, and AADC is another one. How does this actually work in our institution? I'm just using this as an example. The AAV products for in vivo are delivered to US frozen, and they're stored in our specialty pharmacy. They're ordered for each patient, because they're so expensive that we don't want to carry them in our stock for any period of time. At the time that the patient is ready for infusion, the pharmacy thaws the product and draws it up in a biosafety cabinet, and we coordinate the time from thawing to administration so that it's quite short. As I said, we don't stock these in our pharmacy, but they're ordered in time to deliver for that particular patient, and most of these are IV administration, other than luxturna, which is retinal and has to be done in the OR, operating room. Pre-medication is pretty simple, and most of these are actually outpatient administered already, and usually the outpatient stay is quite short, and then the patient is followed for potential side effects afterwards.

Ex vivo is much more complicated, so the autologous product, after it's released from the manufacturer, is delivered to our specialty cell laboratory, and that often takes, for the manufacturing release process, 60 to 90 days, but in fact, this is a real bottleneck. So in the United States, the commercialized products like to say this is the timeframe, but it actually tends to be much longer than this. Then, the patient admitted to the bone marrow transplant given conditioning, the product is thawed in the cell therapy facility delivered to the floor for infusion, and then the patients generally in an inpatient for about four weeks, three to four weeks. So let me give you two quick examples. The first is Casgevy, which is an ex vivo gene editing product. Just to remind everyone, I'm sure most people in the room are aware, sickle cell disease is caused by a single base pair mutation that causes deoxygenated hemoglobin S, the mutant form, to polymerize and crystallize the cause of these fibers.

That's the basis for all the chronic manifestations of the disease, most characteristically chronic hemolytic anemia and acute and chronic pain. I'll just make the point, that I'm sure everybody's aware of, but I'll just make the point right now, the worldwide burden is such that ex vivo gene therapy, there's just no way that it could ever be used to address the burden. This is a map that shows you the burden in India and Sub-Saharan Africa of sickle cell in the next four decades, basically. Just to remind you again, these are personalized therapies, so the medicinal product is made for an individual from their own

cells. The other thing about gene editing is that there is genomic variation in the world that may or may not, it's not clear yet, impact the availability of some of these therapies for individuals. And so, the idea for a Casgevy is there's a little bit of an edit of this sequence that we call an enhancer, that regulates the expression of a transcription factor called B cell of an A.

That transcription factor represses fetal hemoglobin in adult cells, so once you get rid of that transcription factor, fetal hemoglobin is now expressed in adult cells, and it's a binary switch, because when that occurs, then the sickle hemoglobin is not expressed. Fetal hemoglobin, in and of itself, is quite potent in inhibiting polymerization. This is the sort of important paper from that work, and on this graph here, you see the total hemoglobin level, and importantly, the hemoglobin F level, which is around 40%. On the right, you see the resolution of vaso-occlusive episodes in patients undergoing this therapy with these kinds of blue triangles hard to see being the episodes of vaso-occlusion quite effective. So you can see substantially reduced hemolysis and vaso-occlusive crisis, but not completely resolved, so all the patients tend to have some residual hemolysis. 6 out of 43 in this study had vaso-occlusive episodes, and the cost is 2.2 million per dose.

The second one is lyfgenia, which is a bluebird product, another ex vivo. Here you're using a lentivirus vector, you can see has been modified slightly, the globin molecule to make it more inhibitory to hemoglobin S polymers. The cells are transduced in a GMP facility, cryo-preserved, and then patients admitted for infusion. This is work, senior author by John here, who probably will talk a little bit about this later. Again, quite impressive reduction in VOE on the top. There are major VOE's and on the bottom, minor VOE's or VOE's. And again, hard to see because of the scale, but you can see the blue dots disappear, basically, with the infusion. Now, this one is interesting in the sense that there's FDA black box warning, because in the early cohort of this study, two patients developed AML. I just would emphasize that the scientific evidence, by the way I read it, doesn't suggest that that's related to insertional mutagenesis, but it caused the black box warning, and the price of this product is $3.4 million per infusion.

Then, how do we monitor patients once they get the commercial product? Well, it turns out it's not uniform. It depends upon the product, and I won't go into a lot of detail, but here's three vignettes. In this study, it's a 15-year follow-up of 150 patients, which includes things like bone marrow biopsies, and analysis of blood counts and vector insertion analysis. In this one, it's 250 patients for 15 years, so you get the feeling it's not simple, and that study long-term, It's also bone marrow analysis, CBC's, and vector analysis, insertion analysis. By the way, mandated but not paid for. It's an important point, not paid for. Then, finally, this one is a little bit smaller. It's 17 patients over 15 years, and then this is one I just want to point out where, in addition, there is an analysis of the genomic sequence, because this may affect off-target effects of this particular product, and so it's, again, not particularly simple at this point. Now, what about the introduction gene therapy in low and middle-income countries? How am I doing on time?

Susan Winckler:

You're good.

Dr. David Williams:

Okay, good. So here's a picture from the cover of Science Translational Medicine, that Mike was kind enough to send me as he was prepping me for my talk, and you can see here, this is people standing in line for cure. The question is, how do we get from the technology that we've developed to more widespread access across the world? So let me give you a couple startling facts, or at least to me, maybe

not to you. There's estimated to be over 500 phase one to three gene therapy trials in progress, of which about 300 are genetic as opposed to infectious disease. None in Africa, India, or Brazil.

Since 1994, there's been 62 clinical trials of some kind of gene therapy for HIV, and there's been none in Africa, so right now we're not doing very well, with respect to introducing this technology elsewhere. Let me talk a little bit about the barriers. One, Julie, you actually mentioned, which is that the current approaches require intensive inpatient treatment, and that's not available in large parts of the world. The manufacturing is complex and individualized, at least currently, and that requires shipping, storage, and administration. I kind of reviewed that. Regulatory, it's already been mentioned. There's a lack of harmonization across regulatory jurisdictions, and really, to me, cost. I mean, it's not sustainable, even in our country at the cost that we currently have in my view. Then, importantly, Julie mentioned this too, community acceptance. Let's dig down a little bit in these. Right now there's a lack of equitable access to healthcare in many parts of the world, including parts of the United States. And in in particular, large portions of the world are still rural, whereas the tertiary care centers are really centered in large cities. And so, one could imagine potentially that we need to develop a hub and spoke structure where some things are done centrally, but then distributed back to rural areas for follow-up, for instance, and other parts of the healthcare.

We actually do that already in Boston, so we see patients from all over the world. Part of our analysis is asking before we do anything, once there is gene therapy, is the person going to be able to go home and get the adequate follow-up care that's needed?

Manufacturing. There's even in this country, still a global shortage of manufacturing. It's a bottleneck. And so, even at high income countries, this is an issue. Low and middle income countries may very well need to have a plan where short term, they outsource manufacturing, but invest R&D in developing their capabilities in the long term to do central or to do manufacturing locally. And then an alternative to this is the carrying cross approach, which is the, to develop affordable licensing fees, that can be accessed then by low and middle income countries, or to develop point of care manufacturing, which might reduce significantly the cost.

Finances are a real issue, I think, in my view, the real issue right now. That's may require some sort of collaborative approach with philanthropy and government funding, which is Gates Foundation approach. But it will still require priority setting by local authorities. By that, I mean, you think about a high cost security therapy for one individual versus having penicillin available for thousands of children with sickle cell disease. And also often not thought about is that the cost of the burden of chronic disease, needs to be calculated into the thought process. But the problem with that is usually the price setting and the costs are determined by short-term goals, not long-term goals. I mentioned point of care manufacturing. I think that's a real area that will reduce costs in the long run and investment in local manufacturing.

Regulatorily, I think there's real possibilities of having some progress in this area. So, there's an opportunity for regional harmonization already, for instance, the Africa Medicines Agency, which could potentially lead to a continent level agreement. This is already in place in large part in the EMA, for instance. Ideally I think an international framework for regulatory oversight would be helpful. Another idea that's been used in the UK for this is, what we call an, N-of-1. A hospital in the UK can do gene therapy on a limited number of patients, without a lot of regulatory oversight. And this reduces the cost of the initial investment. Globally, develop harmonized regulatory requirements and processes, maybe even have central global review processes adopted by all countries. I think really important is to provide education around best practices, in carrying out an oversight of gene therapy. So, from the very beginning, have that as a goal.

And community buy-in, so early involvement of community groups and planning and implementing trials. This is already being done in HIV and the Joint Adherent Brothers and Sisters against AIDS in Africa, and the National Alliance of Sickle Cell Organizations in India, with a focus on community education.

What does the future hold? Can we envision gene therapy in a vial? Mike mentioned this. He may not remember, but about a decade ago, he came to me, I don't know how he found me, but he found me somehow. And he says, "Dave, what about in vivo gene therapy?" And I said, "I've only got 20 years left in my career, I'm not sure that's going to work." And he says, "I want you to do it." So, we've been working together. But the idea is of one shot, single dose therapy, I think we have to develop and implement less toxic conditioning or some sort of effective in vivo selection. And I think you're going to hear more about that this afternoon, actually.

There needs to be critical infrastructure to allow equitable access to healthcare across rural populations and under-resourced healthcare areas. And developments of funding models that recognize the long-term savings in patient resources and importantly in patient suffering.

In the last minute, let me just talk to you two or three slides about what we've done institutionally at Boston Children's. We start out by identifying our clinical physician lead and product champion. We feel like that's absolutely critical to get where we need to be. Someone of our MDs, someone of our docs has to say, "This is something that's really important to the patients I care for and I'm going to work on it hard." And then we draft a patient workflow or model for care delivery and we establish a stakeholders group where, every person or every group in the hospital that's going to touch that patient, is involved as soon from the beginning as possible.

And then for the sponsored programs or commercial products, we establish a point of contact as a liaison between the institution and the company. I'm not going to go into a lot of detail, but we think about these three pillars. Education to everybody involved, including patients and families, communication so that everyone is understanding where we're at in the process, and operations, which is defining who needs to be involved in delivery of that particular medicinal product to the patient.

And at the center is the patient. We have to think about the referral site capabilities and the follow-up plan. We have to think about the nonclinical support, psychological and otherwise, we have to think about, payers and what they will pay. And then we have to think about the fact that in ex vivo, at least gene therapy, oftentimes the patient actually has to relocate for six months into a local institution and then afterwards they have to get back home. And so, our blueprint is organize the institution, standardize as much as possible, and establish relationships in the institution, legal, disease center leaders, patient care and clinical operations, and of course finance.

And that's allowed us to run multiple, both clinical trials, and now run multiple commercial products, as quickly as we can to help the patients that have really terrible diseases. In there, I do just want to give a shout out to the gene therapy program at Children's. It's run by Dan Bauer and Christie Duncan with Colleen Dansereau, who's helped with the last slides. But you can see we have a very large team, mainly made up of clinical investigators who are those champions for the different diseases. And we work with a lot of companies and a lot of key partners shown here. I'll stop there and-

Susan Winckler:

Fabulous.

Dr. David Williams:

Yep.

Susan Winckler:

Let's thank Dr. Williams. It's precisely what we were looking for in that overview of the current construct. And we'll be having Dr. Williams back to the stage in our second session to have discussion among all of our speakers from this first session. Thank you. And we'll turn now to our second speaker. Dr. Karikari Boateng is joining us virtually, and so I want to make sure that he is set and ready to go. Um, Dr. Karikari Boateng is Director of the Center for Laboratory Services and Research at the Food and Drug Authority in Ghana. And this is our opportunity to learn directly from a regulator, in this case from Ghana, to talk about the current state of the knowledge of gene therapies in low and middle income countries. And share with us some thoughts on what is needed to gain acceptance of these novel therapies for patients in these countries.

Dr. Eric Karikari Boateng:

Good afternoon everyone. And good morning in America. My name is Eric, and I'm going to talk to you about the current state of cell and gene therapy, in the lower and middle income countries using Africa as an example. Next slide, please. Please can we go to the next slide? Mine seems not to be changing. Thank you. This going to be the outline of my presentation. As a regulator, definitions are very, very important. First we will look at the definition of cell and gene therapy as what pertains to the US-FDA, the European Medicine Agency, and then the World Health Organization and the current regulation of cell and gene therapy in LMICs with respect to Africa. Next slide.

The perspective of LMICs for acceptance of cell and gene therapy. The challenges, the way forward and then conclusion. Next slide. And I'm very happy because Dr. David Williams has given us a very good background of gene therapy. Regulatory wise, gene therapy is a technique that modifies a person's gene to treat or cure disease as you get sick. And that's how the US-FDA defines it. Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

When it comes to Europe, they call it advanced therapy, ATMP, that is, Advance Therapy Medicinal Product. And then they tell you that these are gene cells or tissues, which maybe engineered that can be used to treat disease. Can we go to the next slide?

Next slide. And then this how WHO defines it. Also they call it ATMP. That's any cell or gene therapy product or tissue engineered product, that has been substantially manipulated or performs different function in recipient than in the donor. And this is a reference of how WHO defines cell and gene therapy. Can we go to the next slide?

And then, WHO also goes further to have a definition for cell therapy. That's a product composed of human nucleated cells intended for replacement or reconstitution, and/or for the treatment or prevention of human disease or physiological conditions, through the pharmacological, immunological or metabolic action of it's cells or tissues. But then we can know that most of the deficient seems to be aligned, but there are some cases whereby there are some products, something like Lantidra, these are pancreatic eyelets. The USA-FDA did not classify it as a cell therapy, whilst when it comes to the EME and other parts of Europe like that, they don't classify that they consider it to be just part of transplantation. Can we go to the next slide?

And how does the World Economic Forum describes cell and gene therapy? They'll tell you it's the use of a genetic material to treat or prevent disease, involving the production of the genetic sequence into cells. In vivo or ex vivo [inaudible 00:47:54]. We can see that almost their descriptions are very much in aligned with what Dr. Mark just told us now. Can we go to the next slide?

So with this let's shift it because Dr. Mark has spoken about this. I mean, cell and gene therapy and mechanism of cell and gene therapy. He just described so, can we go to the next slide please? There's no need repeating it.

In mid-2022, there were more than 2000 gene therapies worldwide, and look at the therapeutic areas, oncology, neurology, blood, and cardiovascular. But then the question that I'll ask is, how many of these therapies or how many of these clinical studies take place in the LMICs? That's the question that I'm just asking too and he just said it's practically none. Almost of all these 2000 [inaudible 00:48:50], you'll see that it's only four that is taking place in Africa. And even out of that four, in Africa it's so clustered. It just clustered around both Egypt and then Egypt to the north and then South Africa to the south. Can we go to the next slide please?

As we just said, clinical research remains in a High Income Country, while the LMICs carry about 90% of the world disease burden. And this according to the World Economic Program report in 2022, on Accelerating Global Access to Gene Therapy. Can we go to the next slide?

And then, this data on clinical trials, from 1991 to May, 2008. Just look at it. Worldwide, there are about 274,000 clinical trials and ow many were taking place in Africa? Just 7,192. And if you go to the Pan-African Clinical Trial Registry, you'll see that this figure only starting getting better after the year 2006. From 1990 to 2005, we barely did not see any trials at all. And these 7,192, it represents about 2% of the... As I've said, is that take place worldwide, majority of them, about 70% of them, is shared between Egypt to the north and North Africa, and then, South Africa to the south. But they really come to the WHO [inaudible 00:50:17], Egypt is not classified as part of AFR, but the Eastern Mediterranean region. If you can look at the WHO [inaudible 00:50:27], they're not even part of Africa. Can we go to the next slide?

Again, looking at the World Economic Forum, from their report from 2022, you could see that for about 1,000 gene therapies that are going on, less than 5% were recruiting in LMICs, excluding China, with only four trials in Africa. And this you'll know that basically Egypt, South Africa. You can see, since time immemorial, studies have not been taking place on the continent, why? I don't know. But I can say, before WEF in 2006, much was not being done on the continent. But after that, a lot of capacity has been built on the continent and that's why we see the normal trials rising steadily.

And just about two years ago here in Ghana, we had the opportunity to authorize a first in human clinical trial. But of course that was a vaccine, not a gene therapy. And that study has just been completed. It's a vaccine against Lassa fever. Technically what used to happen 20 years ago is not the same. So I think the the time has come for the world to look at it that, yes, I mean, the LMICs might be lagging behind, Africa might be lagging behind, but a lot of infrastructure has been built to encourage studies to take place on the continent. Now go to the next.

That's the current state and understanding of cell and gene therapy in LMICs. We are 55 countries in Africa, that's if I add Sahrawi Arab Democratic Republic. And out of this only six have attained the World Health Organization benchmark of Maturity Level 3. That means to tell that they have world functional integrated regulatory authority. And these six countries are Egypt, South Africa, they're for vaccine production, Ghana, Nigeria, Tanzania, and then recently, Zimbabwe. You can see that, revolution of medical product and then clinical product authorization still remains a challenge on the continent.

When it comes to cell and gene therapies, as regulators, you need guidance documents and you need guidelines and sometimes you need regulations. Like, you need regulations. But then, most countries on the continent practically don't have guidance documents or regulation. And you can trace that to the fact that, because most countries rely on the WHO technical reports and then WHO guidelines, since WHO is yet to develop it, you would see that, most countries will not get. They will wait for WHO to develop and then they adopt, as it normally happen.

And for the countries that have cell and gene therapy, most likely it'll end up being regulated as a biologic. Your character is biologic. Now we'll go to the next slide.

As we all see, and the slides that are coming really soon, the LMCIs especially Africa, carry the highest burden of the disease. But then, there's very limited access to clinical trials and even to products that are needed to cure these diseases. And that's why I'm saying, there's need for cells and gene therapy in LIMCs. Since biological and genetic diversity varies widely across population, countries cannot solely relied on gene therapy developed and tested abroad. Yes, because it might not always be the same. No. The genetic constitution might not be... There might be some mutations or some single nucleotide polymorphism which might differ. And that means one therapy that might work in the high income advanced work, might not work. And you don't have to wait for the studies to finish and then the medicines to become cheaper before you introduce it. Yeah, maybe it might work in the HIC, but there possibly it'll not work in the LIMCs. So, it's better for development to go on in tandem. Next slide.

This is a case study that I just developed to present. If you look at Uganda, the HIV prevalence is 5.5% in adults, and the global average is 0.7. About more than 15,000 children are born annually with sickle cell. In Tanzania, look, 11,000 babies born annually with sickle cell disease. In South Africa, 6.7 prevalence of Human Hepatitis B Virus, 7.2 million people living with HIV, and 24.6 out 100,000 males born with hemophilia A. In Thailand, that's three to 9% prevalence of beta thalassemia among newborns. In India, more than 1 million new cases of cancers are diagnosed every year, and accounts for 8% of the world cancer patients. Can we go to the next slide?

We can look at the epidemiology. Yes, we can see that from what we just showed, the LMICs carry the highest burden of disease, but, when it comes to trials and then access to this very important therapies, it remains a mirage. These are these five low and middle income countries, Uganda, Tanzania, South Africa, Thailand and India were examined in a case, to identify essential areas for capacity building to support long development and delivery of cell and gene therapy in LMICs. From what we could see, we could see the HIV, Hepatitis B Virus, sickle cell disease, beta thalassemia, hemophilia and some oncology disease are really a challenge. With high disease burden, [inaudible 00:56:22] need for with respect to therapy. Next slide.

With what we just presented, what will be the way forward to ensure that LMICs, especially Africa, get access to clinical trials? Yes, we might not have the money, maybe, yeah. Most countries might not have the money to subsidize or provide this therapy after it gets marketed towards high income nations. But that doesn't mean, said should be excluded from clinical trials, whilst they seem to carry the highest burden of the disease.

Looking at the way forward, one of the good things to do is the development of regulatory guidelines. Guideline or guidelines for ethics committee and NRAs, to have the ability at least to know, to have the concept and the framework, to regulate this really complex therapies. And of course there's the need for appropriate patient and public education on the various aspects of cell and gene therapy.

Why would I say this? If quite remember, during the Ebola crisis in the Mano River Union, that's from between 2014 and 2016 in West Africa, that's Liberia, Sierra Leone, and Mali. I think in Ghana we approved the phase two A study, no, the phase one B study for this viral vector at 260, that was the prime and then the Modified vaccinia Ankara as a boost. And there was a hullabaloo. People they cannot say, "Why were we going to kill our people? Because the disease is not here and we want to try a vaccine," which is very dangerous because of, lack of understanding. They didn't know that it was the viral vector. That was just had the transient for the Ebola glycoprotein but not the live viruses of. When it comes to the LMICs education, public education is something that is very key that must not be toyed with at all, because it can easily kill a very good product due to misconceptions.

And then high quality studies exploring patients and public opinion and experience of cell and gene therapy are required. Of course, the capacities to ethics committees need to be built, in clinical trial authorization for cell and gene therapy. Because, before even regulatory authorities will authorize clinical trials, they'll ensure that they have ethics approval. If the ethics committees themselves don't understand what cell and gene therapy, then how then would they authorize that?

Then another point to look out is, building of regulatory capacity and the provision of training, and other means of supposed to LMICs in strengthening regulatory systems and then staff. And of course we know that this cannot be done individually. Like, in the case of Africa, there's African Vaccine Regulatory Forum. Yes, initially it was formed to target vaccines, but now it has spread to cover medicines and other medical products. And it covers almost all the 55 countries on the continent.

If capacity is built to have AVREF, it would be equitable to be distributed to, almost all the countries on the continent or something that is done. And AVREF is the technical wing for clinical trials for the African Medicine Authorization. With respect to clinical authorization, going to AVREF that means to lead continent. And for maximum authorization, one is go EMP, that's the Evaluation of Medicinal Product Technical Committee, or the African Medicine Agency. That also means, it's going to cover the whole continent.

And then of course, we should insist that we should have international regional, and the national guidelines on cell and gene therapy that's covering a wide range, including good tissue practice, good manufacturing practice, and then tissue traceability. In order to that, this will lead to harmonization and then prevent delays when authorizing clinical trials and then, maximum authorization. Next slide.

Then technical assistance, especially from the high income countries, especially the US-FDA, EMA to these low income countries, when it comes to clinical authorization. WHO has a policy that to calls to rely on, yeah, you can rely but is it everything that you can rely? Sometimes you might need technical helping to be good for this thing to be pull off. Then that's what I've talked about, reliance. Then funding the exploratory gene therapy R&D appropriate for lower and middle income countries infrastructure.

As Dr. Julie Makani said, yes, there are some clinics in Africa now which we feel are in the position to develop and then administer this therapy under clinical trial and under supervision of NRA and ethic policy. Now go to the next slide.

What we see now for the way forward is, there need to be encouragement in LMICs to building site infrastructure and training of investigators so that they can build the capacity in order to, at least conduct clinical trial for this all important therapeutic area. Yes, but that we'll always say, we might not be able to procure, but that doesn't mean we have no sites that can conduct this clinical trials. [inaudible 01:01:44], South Africa, Tanzania, Uganda, and Nigeria, have really now put in national policies to conduct studies in this area and the whole world should look at it. Over. Thank you.

Susan Winckler:

Thank you. Thank you. Dr. Karikari Boateng. I was struck with your 10 points of thoughts on the way forward and you pulled through our themes on collaboration, education, integration, and then the call for additional clinical trials, which leads us to our next speaker. I'll invite to the podium, Dr. Kwasi Nuako, who is Coordinator for the African Vaccine Regulatory Forum Secretariat, with the World Health Organization Regional Office for Africa.

If you would pick up this thread in talking about clinical trials in Africa, that would be great. We had such an excellent setup, I'll turn it over to you.

Dr. Kwasi Nyarko:

Thank you very much Susan. And good day colleagues. I'm happy to be here. Most of what the previous folks have said, basically scoops my presentation. So I don't have to say much, they have said everything. Oh, next slide. Basically, I'm going to be talking about, it concludes in a strategic approach forward. A lot of the background has been provided by the previous speakers, so I would basically talk a bit about the ecosystem for clinical trials on the continent. What we are doing. This picks up on many of what has been said by Eric, as well as Dr. Makani. Next slide please.

Not so much to say more than this in a sense as simply, the entire clinical trial capacity activity on the African continent is less than 2.5% of a global activity. This has been mentioned, you just heard it. And out of this, and this would be for all clinical trials, out of this gene therapy would be quite low. That being said, there is a lot of potential. Next slide.

This is just to give a little bit of context about what's going on on the continent or how though there are some folks that are Afro positive, how they are positive Africans look at Africa. We do have a population of 1.5 billion people right now, making up about 20% of the world's population. With a median age of 19 years old, which is quite significant. Made up of 3000 distinct nations, so there is a wide genetic diversity that is useful, when we are talking about what we're talking about. There is an African continental free trade zone that's actually looking at creating the entire continent as one marketplace, with this young population.

And so, for the future, all therapies that are being developed and stuff, you're really looking at, any serious person not really to ignore the continent. It's estimated that by 2050 the population would be 2.5 billion, at the stages it's going. And that would be the combined population right now of India and China put together. The African Medicines Agency and its impact has been mentioned by previous speakers, so I'm not going to say much about it. Next slide please.

I'm representing African Vaccine Regulatory Forum, which doesn't deal only with vaccines, but it was a forum that was established by the WHO encouraging African countries in 2006. And as the previous speaker indicated by up to 2006, there wasn't much clinical trial activity. And this forum was established by various countries at the time, having clinical trial applications, that didn't really know what to do with them. Therefore, the countries got together, and through WHO helped each other. This is when it was established, they used a network approach to basically help each other in building capacity for clinical trials. But in Africa, for the clinical trials, actually before regulatory agencies, clinical trials were approved by ethics committees, which is still there.

On the continent, we look at both, next slide, we look at both the ethics committees and the NRAs actually work together. And so for our capacity building initiatives, we're doing both. And in most countries you can, regulators alone cannot actually approve clinical trials or even... That's the situation we have. The objectives there, I would focus on patient safety, because it's clear for that here. Innovation and research is important with...

Next slide. One of the things that usually folks talk about on the continent would be, "Oh, it's too slow. We don't have the infrastructure, it takes too much time," that kind of stuff. It's not universal. I mean, if you take the averages, maybe you would get it, but there are pockets and there's a lot going on that... This is a survey that we did 2008, no, about 2021 or something. No. Yeah, 2021. In terms of capacity, because we look at capacity, this is a survey done by Boston Consulting Group, quite detailed, looking at the processes and the tools in terms of governance of ethics committees and regulatory agencies, infrastructure and so on and so forth.

Bottom line, there are processes in place. Most countries have regulatory systems, but there is a human resource gap, basically, having expert reviewers, that is a challenge. Digital infrastructure to manage things is also a bottleneck, which we are working on.

Next slide. It shows in the, when we talk about the maturity level, which was mentioned. But in terms of the needs for the continent, globally, it's clear the clinical trials phase one, early clinical trials on the continent is quite low. We need to do more of that. We need a strategic approach to human resources to be able to... Not every country can become your ML3, we need efficient processes and collaboration is essential in going forward.

Next slide. This is probably a repeat of that one, so go on to the next slide so that I can focus on other stuff. If you look at the maturity level of the countries, in terms of regulatory capacity Eric has mentioned, the colored ones are really what falls within the African sub sub-region. But Egypt is also, in terms of the continent. The ML3s that's the regulatory agencies that are fully functional are the ones that are in green. Then you have those in blue, that ML2, that's working towards it. And majority of the countries do not have that, but it does not mean they may not be able to do anything. But the distribution is there, and folks are working. And most of these were assessed maybe from about 2018 forward. Next slide.

The latest one we got was Zimbabwe, which was just in May, which got the ML3 designation. Over the past 18, 17 years of regulatory capacity building, there has been significant increases as we've said. Harmonization has actually increased a lot because, in terms of what we're doing, we're working on common processes, common guidelines, tools, reliance. But this is also limited, if you look at the entire context. So, how can we make this better? Next slide.

This is more about sickle cell. I think it's been mentioned that, yes, there is a high disease burden, but in terms of studies we don't have as much, so go forward. Others have mentioned this so I'm not going to dwell on this. Next slide. In terms of the forum that I work with, AVAREF, this is what we do the most. We're doing capacity building, all levels of capacity building for national ethics committees as well as regulatory agencies. What do we do? We do a lot of training of reviewers. There is fundamental training, there is specialized training, be it biostatistics, advance designs. We even have a small group that we're forming for cell and gene therapies. The ethics committees are involved. We're building digital platforms that they can use. We're working with all partners that would help. We work with regulatory agencies such as the FDA, EMA. They do help in capacity building.

In terms of the training, we have what we're calling the trusted expertise are various experts that lend support to countries that need it. We have a roster of experts there. In terms of emergency preparedness or emergency registries such as the MPOX that's happening right now. We have the 13 high-risk countries that potentially impacted by MPOX have nominated reviewers and currently they are reviewing this, the vaccines that are available. We are actually working together with the help of FDA, EMA and those who have approved it as well as two African countries that have already done it. There's quite a lot of work being done. Vaccine manufacturing is also there. The impact, what I have there on a clinical trial sites, it's important because you can't just look at supporting regulators and ethics committees. We have to look at the ecosystem and as the entire cycle. We are beginning to do that. Go forward. Next slide.

Okay. In terms of what we do to, we do have this network that provides clinical trial, scientific advice for sponsors because sponsors are interested in knowing where they can do their trials. We offer the scientific advice. We also offer joint reviews. When folks are doing multi-country joint reviews up to 17 countries, we're able to organize this. We're supported by BMGF and others. We do facilitated reviews for emergencies such as MPOX that I have mentioned. Next slide. These are some of the things that we are doing, but now let's talk about clinical trials and what we think, or at least what we think about clinical trials. The volume in Africa is increasing and will continue to increase. The need for working together such as, so operationalizing this Africa Medicines Agency would be useful because at the end of

the day most of these countries are beginning to work together, we'll understand in working towards harmonized internationally recognized standards and this would help in pushing things forward.

We also have a clinical trial pilot that we are beginning to put together and this pilot is really taking a number of countries that are probably the most advanced in the ecosystem so that we can have predictability and consistency, I'll talk a bit more about that, to ensure that the timelines are adhered to, that we have streamlined processes and we're going to get high quality advice. Simply said, we have asked the 17 of the strongest countries in terms of regulatory capacity, in terms of clinical trial volume to nominate reviewers for all these countries to work together as one agency i.e. To rely on each other, to rely on their expertise so that a biostatistician from country A can help country B.

We're beginning to do that and I think this will have a significant impact on new trials coming in, on new advances because we'll be able to pull our resources together. We'll be able to have more effective regulatory strengthening, harmonization and this is something that we're doing and I think it's going to help in ensuring that we're able to deal with some of these things, so new advances such as gene therapies.

Next slide. These are the countries that actually that have been in green there that are working together as the network. You will see that you have South Africa, there you have Egypt, you have most of these. It's the geographic distribution is fine. While it's a network, we believe that ultimately working together through these will be useful. Next slide. In terms of strategically, because my main topic here was a strategic approach to doing this. A lot of the basic information has been given. Africa has the genetic diversity. We would have the population, we have a regulatory network, that reliance network that is going to be working together to say that their regulators are ready are able to do this. There is a lot of convergence, even the discussions that we are having here. How do we really harmonize this? How do we leverage this to come up with a strategy?

For an effective strategy, this is what you need. We have the basics there. Capacity building over the last 17 to 18 years has been helpful, has provided a good foundation going forward. You have good centers. There are initiatives where folks are doing surveys of clinical trials sites across the continent. I'm not presenting that here to see who's doing what in terms of what capacity. I think the days where we used to say, "Well you can't really do this in Africa, it's not working, it's out of date." I am working in Africa now. I started working there in September. I was previously working for the federal government in Canada. As an African, I go to African countries and I'm like "Wow, this is not what I was expecting. Things are changing and there is a lot happening," and so I think we need to pay attention. Next slide.

In towards a thriving ecosystem for gene therapies, the previous speaker Eric did say a lot. We need to support the ecosystem. We need to support clinical researchers, you need to support investigators, research institutions, clinical trial sites and also support the capacity building for regulatory and ethics that's ongoing. There is a lot going on that is commendable that you can build on. We're not talking wholesale support like support everybody, because not everybody can do this, but there are places that you can actually put in your investment and be able to see results and also help in this working. In terms of we need to include African clinical trials, African sites in clinical trials for gene therapy, I think we need to look at it. You need to find there are places which can take part in it. Training of reviewers within the NRAs, it's being done and importantly engaging and involving the institutions, the researchers, the communities.

We're beginning to see even... Well, even in North America you have your anti-vaxxers and you have the vaccine hesitancy there. This is not about a population that's not educated or not enlightened. Increasingly, we are having that on the continent as well. I think involving the communities in these studies at this early age for them to talk about it. Gene therapy, what do you call this? Clinical trials, is a way of increasing early access in a controlled environment. Being able to do this is definitely going to be

helpful. I would echo that message that others have provided as well. Next slide. Finally, I just want to talk about these little boxes in the little time that I have.

Research, as you know, you are researchers, in Africa is crucial for developing a treatment that we're going to need. This research hopefully would include Africans. With regard to equity, I think that ensuring that all populations are going to benefit from this would be helpful. Given the fact that we don't have much going on on the continent now, we can make efforts to actually increase it. But then that being said, the whole ecosystem of clinical trials is not that much. We have to choose carefully and I believe we can choose and include the right folks and be able to actually do that. Building research capacity locally would be useful. When I say local, I'm talking about these 55 countries. It's not small, local. This is big local engagement and acceptance. I believe that the sooner we engage folks and people talk about it and benefit from the miracles that science can offer is the more we can get the acceptance and also probably see breakthroughs.

Africans think differently, at least I do. Having diversity, not just as a location, not just like saying I have a site in Africa to make your research proposal look good, but actually to include folks, it's something that is useful. We are continuing to strengthen and harmonize and we will always continue to do that. Having a different perspective helps. I know I have two minutes left, so I'm going to use this, my time. Years ago I was in Tanzania and I saw chickens that had been colored purple, green, red around, little chickens. I was curious why would anybody color their little chicken purple? I asked and I was told the main reason was to trick the hawks because the hawks will never recognize that a purple thing going around as a chicken. To me, that is the essence of innovation is innovation from that point of view.

I believe that including a wide range of researchers, folks that can trick hawks by painting their chickens purple would be useful. That is what gene therapy, that is part of what I think we can do on the continent if given the opportunity and working with establishments or initiatives like ourselves, because we're working with the countries we're working with the NRAs, we know who is doing good work and we can help. I believe ultimately this would be beneficial. Thank you very much. What's the next slide?

Susan Winckler:

Thank you so much, Dr. Nyreko. Now, we know you will know everyone who's been in this meeting if they talk about purple chickens, that you've heard it here as a way to think about ingenuity and creativity. We have one more presentation and then we're going to turn to a discussion among our presenters this morning. For our final presentation, I'll turn to Professor Maneesha Inamdar, who is director of the Institute for Stem Cell Science and Regenerative Medicine in Bangalore. She will discuss the ethical considerations for gene therapies, exploring informed consent and other important concepts, a great natural progression from our regulator conversation, our clinical trials. Now, let's dig in a bit to that ethical component.

Dr. Maneesha Inamdar:

Thank you very much, Dr. Winkler. I'd like to start by thanking the Reagan-Udall Foundation and the Bill and Melinda Gates Foundation for this opportunity to talk to you today, and also all the previous speakers for giving you the background on the science and the statistics. Can I have the next slide please? What I'd like to talk about is the ethics and the choice and access related challenges for cell and gene therapy. This term, of course, elicits a lot of hope and a lot of fear in all of us. Hope because gene therapies promise to support an unmet need, to help us fulfill this need. Fear because these technologies we feel may be used for enhancement rather than treating serious disease. How should these boundaries be set? How do we decide whether something is essential or is just an enhancement? Next, please.

This requires us to look into what the unmet need is in relation to health and the WHO Constitution terms it as "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." That right away tells us that there has to be a lot of subjectivity and a lot of context in how we define this need. Next slide, please. Where is this unmet need? As you've heard, the global gene therapy trial distribution is skewed towards the less populated, wealthier nations, but eight of the top 10 most populated countries are low and middle income countries. These make up about a third of the world's population. Next, please. This tells us right away that there is a discrepancy in global disease burden and trial sites.

For example, if you take the blood disorders or the blood cancers, as you can see from the map, India alone, which has a population of 1.4 billion, has several thousands new cases every year. No rare disease is really rare in terms of numbers. Next, please. What we need to look at is how these approved gene therapies, if they are to be used in the LMICs, what it means. Of course, these are now accepted to be scientifically feasible, ethically acceptable with robust oversight and obvious benefits to society. There are still a few technical loopholes in terms of unwanted effects and the long-term effects not being known. But if these approved therapies are simply to be transferred to the LMICs, what does it mean? Next, please.

Do we really need to have any other considerations? The WHO expert advisory committee on developing standards in human genome editing in its early report said that recognized that for somatic treatments involving human genome editing, there are very few countries which have the pathway translation established and there's requirement for robust oversight and regulation to ensure patient safety and public confidence, telling us right away that the science needs to be in tune with the society. Next please. This leads us to ask in the LMIC, all these therapies that we've heard about, what do they really mean? What does gene editing really mean to us? Obviously, we know it'll treat people with genetic disorders, may eradicate some diseases, but it brings to mind the same question of is it safe? Will it change the nature of being human and so on?

Next, please. But what really is the situation on the ground in this major part of the world population is the lay person doesn't really think about this. The lay person generally would probably say, "I don't know what this is, I don't understand," and may even say, "It's not really my problem. My immediate problem is what we call in India, roti, kapda or makaan," your food, your clothing and your housing. When the majority of the population is worrying about this, how do you get to this translational path taking care of the ethics and the access. Next slide, please.

Is genome editing really a greater cause for worry, then, in the LMICs compared to all the health hazards that are there on a daily basis? Isn't it easier for the lay person in society to think about low-cost treatments such as maybe hydroxyurea? Because thinking about these therapies is worrying about the cost of a tourist trip to space increasing in cost. When are we going to get to that stage? Next slide, please. Now, the question that this brings then is who is driving this technology that is coming to the LMICs and who will use this technology? In terms of the ethics, it's important because this is a rapidly emerging new technology with a long-term impact that is not completely understood and the technology is developed in a rich country setting and transferred to the low and middle income country. This is further promoting inequities because of the increased disparity in the scientific and technical know-how and so on.

Next, please. Also, in terms of use, the mechanisms as we heard for engagement for governance in the LMICs are going to be different because of the diversity that exists, the diverse values, the beliefs, the social and cultural norms, and of course the government system. As we've seen in the case of stem cell technologies, this could promote medical tourism because it's easier probably in for some people to go to unsafe and untested interventions in regions where regulation is weak. There's also the danger of

exploitation by fraudulent use of this technology called ethics dumping, which brings us to how do we control the consent and the access. Next, please. I'll talk a little bit about the issues faced with... May I have the next slide, please? The issues faced with accessing and consenting for this technology. Somebody is saying that the volume should be turned up and they can't hear anything. Sorry.

Issues surrounding consent to somatic gene therapy actually are issues of informed choice. Next, please. It's not just the consent, but the consent or the refusal process and especially in cases where children are being treated, what is the statutory age of consent varies from one country or one region to the other. Also, the way of getting consent because patients usually appear with friends and family and it's a collective decision. Who's going to take that decision to consent or refuse? Explanations need to be in local languages. Doctors generally speak at least four different languages. What are the technical terms and how does one convey them and are they really accurate? Next, please. What is the competence? What kind of disclosure and understanding is required? How much information should one, should the clinician or researcher disclose? Because there's likely to be completely subjective depending on who is going to get the therapy? What kind of comprehension do the participants have? What is their genetic literacy and so on.

Then the question of how do we judge how much the participant really understands? Because this depends on their core belief and values. In general, acceptance to these therapies is directly related to the seriousness of the condition, but it also depends on what other therapies, alternative medicines they may be using. This needs to be understood by the clinician and researcher because that completely changed the way the therapy might be working. Next, please. Another aspect of informed choice is after consenting can one withdraw from the trail, is their voluntariness is their authorization or refusal, and while the comprehension of the study is pretty variable across the world, in the LMICs, always it's important to convey whether the participant is contributing to knowledge production or actually just getting a therapy and whether the therapies that are developed, whether the participant can refuse.

The incidence of refusal tends to be less because of cultural and socioeconomic factors and agreeing to the therapy may be the only way to access the therapy. Next, please. There are very unique challenges of conducting these trials in an LMIC population. Because of the religion, the culture, the traditional practices, they may affect enrollment, they may affect the way the sample is collected. Compliance to follow up can be a problem because there is very limited or no insurance and hence noncompliance is not consequential to the patient. The studies are generally difficult to do in multiple settings. This brings us to the question of access because, for example, in country like India, you get oversubscription in trials, but can the patients or people really access these? Next, please. In terms... Of course, we all agree we know that the cost of gene therapies is prohibitive, as has been discussed a lot.

Next, please. To get access to these therapies, what are the issues facing? Well one is, like I said, insurance coverage for genetic conditions is still a work in progress. In India, low-cost government insurance generally supports infections, or diseases that are more prevalent like cardiovascular disease and so on and does not have rare disease coverage. Where the therapy is tested and where it needs to be delivered can differ and the approval processes get complicated in the rural or less wealthy regions. Of course, every trial needs follow up and the limited infrastructure and capability for storage for record keeping in the medical facilities can make the long-term follow-up in these. All these factors actually are very important to consider if technology is to be transferred. Next, please. To overcome this many efforts around the country ongoing and the first gene therapy for CAR-T was launched in India earlier this year, developed for B lymphomas and B acute lymphoblastic leukemia. But the treatment cost is about a 10th of what it takes in the United States.

Next, please. There are also efforts to develop therapies for sickle cell anemia and both ex vivo and in vivo gene therapy approaches. Next slide, please. Also, there are efforts to develop... Next, please, gene

therapies for the beta hemoglobinopathies at the inStem Center for Stem Cell Research. There is the first gene therapy for a genetic disorder hemophilia A being conducted in India as a phase one two first in human clinical trial. While these efforts are ongoing... Next, please. Clearly there is capacity, but there isn't critical mass and it's important that these limited genetic and clinical workforce can be used for various therapies but can also be applied to personalized medicine, which currently is not a priority. Deprioritizing this can actually perpetuate these existing disparities in the scientific and technical capabilities that exist in the LMICs.

A broad adoption of uniform ethics processes is obviously not going to work in a country like India or in the African nations where you have so much diversity, not just in terms of the genetics but also the culture and the traditions and so on, where people actually may have more faith on their local medical practitioner then understanding the science. In this way it's easy to divert to unscrupulous therapies taking root. Also, there's a lack of uniformity in the diagnosis, in the treatment paradigms and so on. It's not just about money. There are many, many other parameters and factors to be sorted out. Next slide, please. Going forward, how does one take care of these? Because it's not as simple as taking a technology that is developed and transferring it to the LMIC. We need a lot of public engagement and education and empowerment so that even though the technology may be considered safe from the perspective of science and medicine, it's important that society is considered and accepts it in terms of their local context.

Of course, this requires a lot of these outreach and education activities and the capability is very limited in most of the LMICs. But a note of caution is that while capacity-building efforts are done all over the world from resource-rich to resource-poor countries, it's been known that there is a skew in the subsequent deliberations within the LMICs by the force of precedent. Despite the potentially very different local circumstances and world view, we need to really develop our own sense of standards, ethics and guidelines, which work locally. Next slide, please. Finally, to develop good governance policy considerations, this should be based on the current scientific knowledge, yet be nimble because the technology is advancing rapidly in harmony with global action, yet sensitive to local needs must consider the differences in the ethical values, the social priorities, the culture tradition across the nations and must be applicable in multiple contexts.

I think this last point is very important because when a therapy is being developed for something like the blood disorders which are prevalent in another country, the researchers doing the research also need to be considering changing their behavior and their outlook towards how they are developing these therapies. With that, I'd like to... Next slide, please. Just acknowledge the people who have helped me develop this presentation, Dr. Ghosh, Dr. Francois Baylis, and Joy Zhang for the consultation and inputs and Sabuj Bhattacharya and Dr. Ghosh for the literature survey and slides. Thank you in some of the 22 official languages of India. Of course, there are hundreds, many more languages. Thank you very much.

Session 2: Panel Discussion

Jimi Olaghere, Gene Therapy Recipient
David Williams, MD, Harvard Medical School
Eric Karikari-Boateng, MS, Food and Drugs Authority (Ghana)
Kwasi Nyarko, PhD, WHO Regional Office of Africa (WHO-AFRO)
Maneesha Inamdar, PhD, Institute of Stem Cell Science and Regenerative Medicine

Susan Winckler:

Thank you so much, Dr. Inamdar. You can go ahead and take a seat here and we'll have a microphone come up for you. With that I'll invite our other panelists to the stage. Thank you so much for grounding us in the ethical component in dynamics to think through in this context. We are going to have all of our speakers come back up here and this is now if you had those questions that we were writing on the cards, hold them up so that we can get to them. Some of the individuals here you have seen before, just next to Dr. Inamdar, we have Dr. Nyreko and Dr. Williams. Then we have a new face and a voice. I'm going to turn to you first and I also just want to note that also Dr. Bratang is on the line as well. But Mr. Olaghere, I think we're somewhat remiss, but I'm glad we're still doing it in the morning where we want to make sure that we hear the voice of the patient.

You have, I think probably a singular experience to any of us in the room in being the recipient of a gene therapy. While I step up here to look at the questions and gather the additional questions for our panel, would you take a minute, actually take four or five minutes, and share your story and your perspective?

Jimi Olaghere:

Absolutely. Thank you. Good to be here, everyone. I would be remiss without giving you all a brief history on why I'm sitting here with you. I was actually born here in this district, Washington DC about 39 years ago due to, I can't believe it was writing this stuff, the fact that in Africa 39 years ago, my parents in Nigeria did not have access to newborn screening. I was fortunate enough to have parents to fly my mom here to the US. She got that newborn screening here and they come confirmed I would have sickle cell disease. They made the decision of giving birth to me here, which is one of the reasons I'm alive today because I've had the good fortune of enjoying western medicine. But we moved back to Nigeria and eventually I came back. My parents really wanted me to take advantage of all the west has to offer and the disease got progressively worse as I grew older.

You grow old and you have other stressors in your life that tend to make a disease like sickle cell compound on itself. I like to describe it as a succession of time bombs. Literally... Well, not literally, you're a time bomb, a ticking time bomb. For me, in my case it was first "Your gallbladder is going, you have two weeks on these gallbladder, we're going to have to replace it." Then after the gallbladder it's, "Oh man, we're going to have to replace your spleen. You're going to have to take out your spleen. Your spleen is going bad." The disease literally affects every aspect of who you are. Obviously, we all know that the hallmark of the disease is the pain, but we often forget about how it leaves you as an emotional vacuum with the mental side of things.

Aside from just the pain you have, all your organs are in jeopardy. Like I said, one by one, everything starts to go. Unfortunately, one explosion can actually cost you your life. I was fortunate enough to have the intervention of gene therapy at the old age of 35 that slowed and actually changed my life, irreparably, a shadow of the person I used to be from going through this therapy. I can from the top of my mind tell you many times I've been close to losing my life. On the honeymoon with my wife, we just got married. That one was particularly sobering because I just realized, "Oh man, I just brought someone else into this hellhole." Or from having a simple port-a-cath surgery go bad because the doctor did not want to listen to my wife and I that "Hey, this guy. Yes, a port-a-cath is a very simple surgery, but he needs a blood transfusion first."

The doctors say, "Oh, I've been doing this for years. You don't need a transfusion for a port-a-cath." That caused the cardiac arrest that almost ended my life or something as... Because I needed so many blood transfusion, I had developed antibodies that I once got bad blood, that put me in a coma for 24 hours because of the high fever I generated from the blood. The disease literally took a stronghold of my life and I had come close to giving up many, many times. Through some stroke of luck, perseverance, my wife and I decided we lived in New Jersey at the time, and that particular location made it difficult

because of the cold weather. We decided to move down south, which definitely helped things being in a lot more conducive weather. But I had the good fortune of finding this clinical trial, the Casgevy one.

I had actually in an attempt to appease my parents, they had been pushing me like, "Listen, you got to figure out something about a way to improve your quality of life. Things are really dire at this point." We brought my sisters over, we tried to do a bone marrow transplant and unfortunately none of them were a match, which fortunately turned out to be a good thing in the end because it led me to gene therapy. I had listened to my parents and I started doing some research on what could potentially save my life. I was really doing it just for them to leave me alone, really to appease them. I had found out that gene therapy could potentially cure genetic diseases. Duh. I had put a Google alert on with gene editing and sickle cell and unbeknownst to me there's this thriving bubbling cell and gene therapy world that I had no idea that existed. After that research, probably about a year later, I got an article in my inbox about a brave woman called Victoria Gray, who was the first person to have her genes edited to alleviate the symptoms of a sickle cell. Read the article called the doctor, and the next day they call me back and the rest, as they say, is history.

Susan Winckler:

Jimi, thank you. What a powerful way of explaining to us why this work needs to be done and the value that it can provide. And the sidebar that parents occasionally have good ideas is one that we'll also take with us. But I want to invite all of our panelists as we think through this. What a great stage setting. I'm going to guess Dr. Williams that you perhaps hear or see some of this reaction from the individuals who are in the trials or use the therapy. Do you want to add anything or share what you hear in that context?

Dr. David Williams:

Well, I think what you said that struck me, to paraphrase it, it's a transformative therapy. And so for many patients that we've treated, we understand and get the feedback that this is so transformative. But in a way, this conference is highlighting the critical issue, it's a transformative therapy currently available to very few people. And so the work at hand is to figure out how we're going to be able to increase the access of transformation to many other people in the world. And it is such, as it has for you, it changes the lives of individuals in such a profound way that you just want it to have that broad application. It's just not possible right now. That's our goal.

Susan Winckler:

Well, and so that ties to one of the questions that we had online, but it ties I think to that, which is the need for health authorities in other countries to learn about gene therapies and what it is that they can do. So I'd say Dr. Nyarko or Dr. Inamdar, would you want to talk about what works well in that education and how do we do that? Yeah, put the microphone right up. There you go.

Dr. Kwasi Nyarko:

Yes. Thank you for the question and thanks Jimi for putting a human face to this. It's particularly daunting, but even working in Africa where you may hear statistics like, oh, well 500,000 children under five die from malaria. 70% of the burden is sickle cell. And a lot of the times if you read this, it's hard to put a face to it and we sometimes just read these numbers. And so we are talking about millions of people who are going through what you're going through that actually need this therapy. And so with regard to what we can do on the continent and what we are doing, I think the most important thing is really finding the right people who need the education to give to them. We do helping clinical trial reviewers. And I did learn not long ago that if you go to a country and you say, well, I have clinical trial

review, they're going to get all the reviewers there, and maybe you may train people who are not needed in that particular thing because the training is coming.

But if you talk to the right people, so now we don't talk to the countries, we talk to the regional economic groups that represent multiple countries, and at the end of the day, they're now able to get the one or two from a country that actually need the help to be able to do this. So I think it's been deliberate in sort of how we deliver the training and the help that is needed in terms of the capacity building. There are people who probably are primed who would be the right folks to actually train, the right folks that you can help them get over the hurdle to be able to make this a reality. And it's taking the time to look for them and taking the time to make sure we get that right.

A lot of the times when we are talking about clinical trials take one year to approve. Well, if the country doesn't have a reviewer that actually knows this sort of stuff, obviously it's going to take a long time for them to approve it. But if you have the right people, it won't take us long. Of course, there's bureaucracy. So I think it's being selective and being purposeful and also actually caring about the end result. You see, my job in WHO is really to help countries. So I can say, yeah, my job is to help countries. I've just helped the country. I've checked the box. But I think if I just go, well, who am I helping and is this really the right person to help and are we going to get... That is the extra push that I think we need to put in what we are doing to be able to get the result. Thank you.

Susan Winckler:

It should just work I think if you... Yeah, go ahead. They'll control it.

Dr. Maneesha Inamdar:

Yeah. Thank you. So thank you for that perspective. Very important. So in India, of course there's a lot of effort from the government, especially in the National Sickle Cell Disease program and missions to build capacity amongst clinicians, amongst researchers and so on.

But as I alluded to earlier, given the vast number of different kinds of diseases though in absolute numbers, we have millions of patients that have either one of these blood disorders, in actual terms that becomes a very small percentage. So these are called rare diseases, which nothing is rare when your population is sort of 1.4 billion. So while there is a lot of push and initiative to increase capacity in the technical and the scientific terms, we lack critical mass. It's only a few centers or isolated groups that have the capability and have the know-how. So of course, spreading this technical and scientific know-how is very important, but that's going to take some time.

Another aspect of capacity is to build capacity in the general public, the general population through education and empowerment because one major issue we face today is of unscrupulous elements sort of resorting to using unproven or untested therapies. And while, of course gene therapies are extremely expensive, there is always sufficient numbers of people who can manage to afford it. And again, though percentages maybe small, absolute numbers can be high. And how do we sort of prevent those who are gullible from succumbing to these unscrupulous elements? And that really requires capacity building, but capacity building in ways that people will actually understand in a local language in making sure the technicalities are not overshadowing the actual access and social and ethics kind of regulation. So that is something where I think if we can build that capacity, then that would be a sort of good way to stop or hinder the sort of unscrupulous use of the gene therapies in the country. Thank you.

Susan Winckler:

That's great, thank you. Did you want to add anything? Okay. I do want to talk a little bit about there we were thinking about education and how do we expand things. Are there also some policy initiatives that

you think would be helpful? And I think actually each of you mentioned this a bit in your presentations about collaboration having the reviewers. I'd love if you'd provide some thought to what are some policy initiatives that might be pursued with government and then related to that, but separate looking more at the private sector, how might incentives help in encouraging industry to conduct the clinical trials of gene therapies in low and middle income countries? So either from government policy or from private sector incentives. Any thoughts there? Yeah, I knew I could convince Dr. Williams to move the microphone up.

Dr. David Williams:

Incentives are interesting. I mean because I'm a pediatrician, we think about incentives all the time because I don't know if you realize this, but in the United States, 70% of the prescriptions that we write as pediatricians are for indications that have never been studied in children. And so, even in the US, this has been an issue. And then incentive plans, for instance, in Europe that have worked is to say to a drug maker, we will provide you with approval for this drug for adults only if you do a trial that demonstrates its effectiveness in children. And so I could imagine that that kind of a policy could be adopted for commercialized gene therapy products. It's a long stretch of course, and there's many other obstacles, but I think that's a policy that could be worked.

The other policy I think that all of us I think we've talked about is some sort of a regional or global policy on regulatory oversight so that it's in a sense, safe but simpler to get to where you need to go

Susan Winckler:

Safe, but simpler. We might be coming back to that too. A great phrase for us to think about. So any thoughts on incentives for industry or researchers to work in low and middle income countries? How do we provide that opportunity? Does that come up at all in the AVRF discussions? As you are strengthening the clinical trial apparatus because you also want to make sure that it gets used.

Dr. Kwasi Nyarko:

Yes, yes. Well, I guess we probably don't use the word incentives, but it's about encouraging folks. So for example, the AVRF model for the joint reviews, instead of a company having to deal with multiple countries for the same clinical trial, we can pull the countries together, do one review, and that one review is accepted by everyone. So that is a form of an incentive.

In terms of their capacity building as well, we are more or less doing that given access. And so one can look at that as an incentive. But maybe a bit of more talk on the policy part or what would be considered policy. They talk about reliance a lot, I.E. a regulatory agency being able to rely on another regulatory agency's decision. This usually requires laws to be changed, policies to be put in place. And you're dealing with two things. You're dealing with trust as well as the legal aspect as well as the science. Even in real life, for you to be able to rely on someone's decision, you need to trust them. If you don't know them, you're not going to rely on their decision.

So you may even have the law which says, yeah, you can rely on someone's decision. If the people doing the work don't really know the reviewers and those people who made the decision, it's really hard to put it in practice. And so therefore that means that we have to ensure that we establish a structure where these people from different countries get to work together regularly to build that trust among themselves, get to know the dwellers in the ecosystem to be able to actually work together. And that's in a way part of what we are doing so that at the policy level, the policy becomes practical so that they can actually decide that, yes, we know Eric in Ghana, we work with them, therefore we can trust this decision and things like that.

And these are some of the practical things that I think we need to put in place to make some of these policy ideas pragmatic and to, lack of a better word, go viral for people to use it.

Susan Winckler:

Thank you. That's great. Go ahead.

Dr. Maneesha Inamdar:

So I'd just like to update. So in India we have the National Gene Therapy Guidelines that were formulated in 2019, but in this space that's a long time ago. So they're currently very intensely being sort of re-looked at and evidence-based guidelines for every disorder are being discussed and formulated and well along the way of being revised. So that is sort of one aspect. And the other is also a Gene Therapy Assessment and Advisory Committee to sort of advise on these specific aspects of either commercial entities or therapies from outside the country that need to be looked at in the local context because of past experiences of clinical trials being done for therapies developed outside the country, which were not done in a proper way. So there's of course a lot of sense of caution for that, but a lot of policy and guidelines. And working together with the local sort of social and ethics experts is under way for these therapies.

Susan Winckler:

Yeah, please.

Jimi Olaghere:

I do want to add something in this one. If you look back historically the way the West is, if you look back centuries, I think the West is the way the West is because of resources from Africa. So I think it is only fair... And lots of people are doing this, lots of organizations, government, [inaudible 02:00:21] but I think we really need to double down in returning some of those resources to Africa in form of medical advancements. It is staggering the lack of medical advancements on the continent from someone that lived there for a short period of time. There was nothing. Blood transfusions took days to get a doctor to find blood and find a private clinic to do the blood transfusion. So I think, a lot of people are doing that, but I think we just need to redouble down efforts in invest. I think we could do ex vivo in Africa if people have the capital, it's going to be capital intensive, but it's not impossible. Logistical challenges of being the excuse and it's not an excuse, but that's what people say. But we can build roads. To Mr. Nyarko point, those are things of the past. I haven't been there since 2008, but it's changing drastically.

Susan Winckler:

I want to turn to you Jimi to share thoughts on, there've been a lot of questions about how do we make sure that the patients who engage in clinical trials, that it's done in a way that they continue to build trust and then learn about the results of those trials. So maybe could you share a little bit of how you chose the trial that you chose or were recruited into it and what were elements that you think are important to that trust and communication?

Jimi Olaghere:

Well, I was actually desperate for mine. I wasn't recruited, I was desperate and I actually had to be forced to read the consent forms, which is actually not a good thing. It shows you how desperate I was. I think there needs to be guardrails to protect people that are desperate as me to make sure they are actually understanding what they're looking at when that big packet came in the mail from Vertex. I

didn't want to look at it because it was just a bunch of medical jargon I didn't understand at the time. So one of the first things that I'll do is create simpler patient educational materials that would make the patient understand what gene therapy is and what they're potentially signing up for. And even better than just having patient educational materials, I'll have a patient, someone that's gone through the process, explain to them what they're about to embark on would be probably the first step.

Susan Winckler:

Yeah. That's, well, an important reminder, we hear that about informed consent and communication generally, let alone in the gene therapy space. So that makes a lot of sense. And then I'm reminded, Professor Inamdar, that we also want the 50 plus languages in India in the recruitment for the translation available. But what other thoughts do you see when you are thinking about that? Actually, if I heard you correctly, did you say that many times clinical trials in India are oversubscribed? Tell us a bit about that and then also how do you work on the education and the trust component?

Dr. Maneesha Inamdar:

Yeah, thank you. So I must confess that this is information that I've received. I'm not an expert in this area, I'm not a clinician. But I think it's just a numbers game. Like I said, rare diseases are not really rare if you look at absolute numbers, and there are so few efforts and so many patients. So naturally most clinical trials are oversubscribed. But because of limited... So for a patient who is enrolled in a trial to follow up or to sustain is very, very difficult because there is no support system for repeated visits, for loss of maybe pay if they're working, loss of time and so on. So this makes it really hard to go through and have repeated visits and have the follow-up and so on. So that is about sort of the oversubscription.

But about the education, and I think that was your other question about the empowerment, by and large, you mentioned that it's good if you have a patient who's taken the therapy and is talking to other prospective participants. But what you do when you don't have the first patient who's got the therapy or you have very few? You have to reach out to a really large number. And it's not as simple as saying that, look, this worked for me in my context because there's a lot of influence of the culture, the tradition, the religion and what may work for one person may absolutely be taboo, not at all, cannot even be mentioned for somebody else. And that may be as simple as what protocol you followed for generating this therapy or what is the way in which you interact with the clinician or you get the dose of the therapy.

So this is where the cultural differences matter a lot and the traditions matter a lot. So as simple as how do you test somebody, how do you collect a sample, especially in the context where it's maybe a woman or a little female child who has to be examined by a doctor, there can be several inhibitions and several restrictions. So these are some of the sort of nuances that need to be taken care of and a lot of groundwork needs to go into this.

Susan Winckler:

Very helpful. Thank you. And we've got some great, I'll just note in the Q&A, it's also turning into a little bit of a purple chicken conversation and they're coming up with ideas like could we have organizations create podcasts or something that help individuals who have been involved in the clinical research to share their story and provide a broader access to it and some other thoughts about better connecting healthcare systems and payers in all of this. I want to make sure, Dr. Boateng, we know you are still with us, so you should chime in as you find any of these questions of interest. I see that you're unmuted, and so you can go ahead and jump in as we're going through the questions.

There is one question about the importance, and I think it's more of a statement than a question, but they asked about, and this Dr. Nyarko may be to you, but when clinical trials are conducted in certain countries in Africa, then what's the conversion rate? Is there often then an application for that to be approved in that country or is that a gap that we need to bridge to make sure that where the research is being done that then there's pursuit through the regulatory process to actually have access to that product later?

Dr. Kwasi Nyarko:

Yes, this is an important issue that is raised where there are people who are looking at the benefits. So for example, you may do the clinical trial, get the information, and then drug gets approved, but gets approved in another jurisdiction and then folks don't get to see the benefit. I was actually involved in a clinical trial as we do ecosystem assessments, we go to countries, we look at sort of what they're doing and advise on how the system can be efficient. And I noticed in a country they have laws to say that if you do clinical trials there, it's not feasible. So I'm not advising it. But they're saying that, look, if you're going to get a genetic patent or something from it, local people who are involved should benefit.

And I think it's just a reaction to the fact that folks realize that studies could be done and they may not get to benefit from it. And this may be some of the things that policy may help. It's not so much yes during the... And then you have instances where, and it's even here, where at the end of the day during the trial stage folks get access and then as soon as the trial ends, there is nothing. And I think this conversation needs to continue. We need to have this conversation to ensure that ultimately solutions would come.

If we look at HIV when it started, I mean the cost of the therapies were so high that the countries, the low to middle income countries that had the studies initially were concerned if they were going to get access to the therapies. Fortunately, now that's not it. Folks stepped in, there was new mathematics and looking at stuff and making things work. So I think in all these instances, we are going to face it, but we really have to be helpful and find solutions so that at the end of the day, the objectives of these foundations such as the BMGF where everybody counts, will not just be a motto, but it'll be something where ultimately everybody would count.

And yes, these are difficult questions. There are no easy solutions. My only thing is that we just have to keep talking about it with good intent and ultimately we would get there. The fact that you don't have a solution now doesn't mean there is not going to be a solution which leads into the whole dichotomy and that it's either yes or no. Well, a lot of the times it's not only yes or no, it could be. And so I hope that in these instances we will be able to push that and while things are difficult, continue to engage and hopefully we will make breakthroughs. Thank you.

Susan Winckler:

Great. Thank you. Dr. Karikari-Boateng do you want to talk a bit about the important connection between clinical trials that might be conducted in a country and then having a regulatory application move through that country's regulatory review system?

Dr. Eric Karikari Boateng:

Yeah, I mean, naturally when you conduct a trial, no, you conduct a trial, you're set to get together data to support your application for a marketing authorization. But as regulators here, we can only authorize clinical trial we ensure that the study is conducted in accordance with the approved protocol, the IP and then under DC. But then after that, to force a company to come and register CMO to apply for a market authorization that is not covered by law, that is more [inaudible 02:11:31]. But then naturally we expect

that if you conduct a trial in the population and the results are positive, the good thing to do is also to try and then apply for a marketing authorization in that jurisdiction so that people can have access to the product or the medicine in [inaudible 02:11:55].

But then of course, that's why some ethics committees also put in what they call post access, where they tell sponsors that, okay, after the trial before you seek for market authorization, how many years are you going to make sure that people who participated in this test get the benefits of this drug? That's more of ethical, but there are no concrete loss binding and sponsors or companies to seek for marketing authorization after they've collected their data from the clinical field program.

Susan Winckler:

Great, thank you so much. An important note that as regulators, the regulators themselves are unlikely to have authority in any jurisdiction to compel an application, but if it's a policy or an incentive perspective, that might be helpful.

We have just a bit of time left, so Dr. Williams, I want to give you a chance if there's one additional thing that you'd like to just share as we've been talking this morning, a thought, an incentive that you would bring to mind as something we could consider. And then Mr. Olaghere I'm told that I should ask you about climbing Kilimanjaro. So we'll do Dr. Williams, apparently a Kilimanjaro story and then we'll break for lunch.

Dr. David Williams:

No, I don't think I have anything profound to add. There's a daunting task in front of us, which is on multiple layers. Regulatory is one. It seems to me that that's something that's reachable, technical. So being able to transfer highly complex therapies into an environment where there's a discrepancy between advanced medicines in some places and rural populations in another. And then I come back to what I said multiple times, which is economics. So the price of these drugs are inhibiting access in other parts of the world. And so I think having the technology drive price reduction so that it becomes affordable has to be done at the same time as the other things are being addressed.

Susan Winckler:

Which will be really helpful as we come in, we're going to close the day with the session talking about all of those dynamics. So thank you for teeing that up for us. Jimi, before we go to lunch, what should we know about climbing Mount Kilimanjaro?

Jimi Olaghere:

Right before Kilimanjaro, I want to make one statement-

Susan Winckler:

Please.

Jimi Olaghere:

... in regards to gene therapy for sickle cell in particular, it's called a one-time treatment. And I think we all harp on that word one time and we forget that there needs to be a holistic approach. One of the gaps that I've seen in my personal life with going through that one-time treatment is there's a lack of support post-transplant, and that is very important. People forget that, at least for me, you're living with sickle cell and your goal is basically to survive. And when one day you do survive, you realize you're not

equipped to live and you have all of these emotions and anxiety. So I wanted to quickly mention that because we have a lot of people in the room that can work on that is to start moving from a one-time treatment to a holistic treatment.

And in regards to Kilimanjaro, the therapy has completely changed my life. I'm a shadow of the person that I used to be, mentally, physically. That I'm able to go and to bring the whole story full circle, as Dr. Nyarko has said so brilliantly that there still needs to be resources in Africa, even though we're seeing progress. Till this day in 2004 there's still lack of access to simple things as hydroxyurea newborn screening. So I got invited to partake in this campaign where we raised a million dollars and we've completed that challenge to raise the money to buy newborn screening for people living in Sub-Saharan region of Africa. And in accompanying with that fundraise, we're going to climb Kilimanjaro. As you know, someone with living with sickle cell you're not advised to go over 5,000 feet and two weeks ago I did 14,000 in Colorado and pretty positive I'll be able to submit 19,000 in Kilimanjaro.

Susan Winckler:

We are going to be ready for that. Thank you so much for grounding us this morning in such a wide range of information that we needed for our subsequent conversation. We are going to break for lunch. So for those I will note we are going to start back here at five minutes to the hour, so at 12:55 Eastern, because we have so much to cover this afternoon. Lunch is provided out here for those virtually we do not have lunch for you, but we hope you enjoy the break and we will see you back here at five minutes before 1:00pm Eastern.