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State of the Union on mRNA Clinical Trials

Announcer:
You're listening to *Innovations in Medicine* on ReachMD, sponsored by Moderna. This is a non-certified educational series produced and controlled by ReachMD and is intended for healthcare professionals only. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Innovations in Medicine* on ReachMD. I'm Dr. Charles Turck, and joining me to take a look at clinical trials that are exploring the application of mRNA therapeutics is Musaddiq Khan, who's the Vice President of Therapeutic Area Solutions in the Customer Value Team at Medable. Mr. Khan, thanks for being here today.

Mr. Khan:
You're welcome. Thanks for having me.

Dr. Turck:
To start us off Mr. Khan, would you give us an overview of the clinical trials being conducted that involve mRNA technology?

Mr. Khan:
Yeah, so there are currently over 200 active interventional trials that are listed on clinicaltrials.gov. And these are across a range of therapeutic areas, including diabetes, ulcerative colitis, and of course, oncology and infectious disease.

We've seen that since the FDA approval of the COVID-19 mRNA vaccines, there's been a renewed kind of prevention and treatment expectation for cancer breakthroughs using this technology. And we've seen in the literature as well that the number of mRNA vaccine-related papers in PubMed, for example, spiked from around 150 In the last 15 years to more than 1,000 in 2021. And there have been over 500 in the first half of 2022.

Dr. Turck:
And what key findings do we hope to see from these clinical trials?

Mr. Khan:
Well, the majority of the trials that are currently listed are phase 1 and phase 2 clinical studies. So the focus for those at the moment is really for the phase 1 studies to demonstrate safety, and in phase 2 to continue to demonstrate safety and also show efficacy. And these are in relatively smaller cohorts before moving in to much larger phase 3 studies, which are conducted in thousands of participants globally.

So the focus at the moment from what's listed on clinicaltrials.gov, and the majority of the studies that are ongoing, is really to prove that in the different indications that these technologies are being studied and to prove that they do work and that they provide a significant therapeutic benefit.

Now, it's important also to note that the therapy is based on RNA molecules, they've been researched for decades. And there was promise in, kind of animal models initially. And, you know, research on mRNA vaccines started in the 1990s with the first mRNA flu vaccine that was tested in mice.

But despite its promise, there have been some technical challenges with advancing mRNA vaccines as a treatment, particularly around how to deliver intact mRNA into cells. And so really, the focus on the work that's going on now is to demonstrate the use of these new lipid nanoparticles as a non-viral vector and to show that the mRNA can be delivered as needed, and demonstrate therapeutic benefit.

Dr. Turck:
How might some of these advances impact the application of mRNA based delivery of protein therapy in gene editing?

Mr. Khan:
Well, I think as the safety and efficacy continues to be shown that the paradigm of treatment shifts, right. So you have new tools in the armory against a range of diseases. And one of the key benefits of mRNA vaccines is their relative simplicity, but versatility, that makes them an attractive treatment modality. The mode of action, they're very sophisticated, they work like an assembly line, and can be very specific. And so, with the continued bigger focus on personalized medicine and targeted care, the mRNA space lends itself well to that personalized medicine approach.

So as the research continues to grow, and as the safety and efficacy is demonstrated, we can see that this technology could be used across a range of different therapy pairings.

Dr. Turck:
For those just tuning in, you're listening to *Innovations in Medicine* on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Mr. Musaddiq Khan, about clinical trials investigating mRNA technology.

So Mr. Khan, if we switch gears a bit and look at this in the context of impact on clinical practice, what are some barriers to the broader application of mRNA technology?

Mr. Khan:
So I think that there are kind of three key pieces that we need to consider with mRNA. Particularly, firstly, around the manufacture of mRNA vaccines. There are kind of three distinct steps. There's the synthesis, the purification, and the formulation that the vaccine manufacturer needs to follow in each of those, of course, has sub steps.

So it currently takes a long time for the synthesis, particularly around kind of neoantigen synthesis. On average, it takes around 160 days. And if we think in the context of cancer therapies, you know, waits of 160 days could potentially reduce effectiveness. So participants genome, tumor genome may change within that timeframe. So really, there needs to be an improvement in the opportunity for screening and identification not only of the antigens, but also then of the manufacture of the mRNA vaccines.

But then the second piece that I think is a significant challenge, and we've seen this also with the deployment of the COVID mRNA vaccines is around the storage. So the quality of these vaccines is highly sensitive to temperature. So you know, storage and transport under a defined temperature range all the way through to administering the product. So from production all the way through to administering the product is important for efficacy.

So there's usually a cold chain needed. So for mRNA vaccines, for example, they need to be kept at between minus 80 and minus 20 degrees Celsius, compared to other types of vaccines that can be stored at 2 to 8 degrees Celsius. That's a significant effort. And so, a lot of that is driven by the instability of the lipid nanoparticle mRNA system. So that can be a challenge for deployment.

And then the final piece is, you know, along with the manufacturing and the storage is around the perceived safety profile. So we were able to see a significant number of doses administered across a large volume of participants with a COVID vaccine rollout. But even there, we've seen some severe adverse reactions. And it's still unclear on what the pathway to these may have been, or they're not deemed to be significant compared to the number of people that have received the vaccine. But there's still questions that need to be understood better around what drives some of these particular pathways, and some of these severe adverse reactions.

So I think those three pieces around the manufacturer storage and safety are considerations that need to be made before this could be part of standard clinical practice.

Dr. Turck:
Now there are any other strategies you recommend to reduce barriers to the broader application of mRNA technology?

Mr. Khan:
Yeah, so I think you know, along with kind of thinking about more efficient manufacturing and supply chain processes, understanding how to improve stability of the nanoparticles, and the non-viral vectors, I think there's also an opportunity to be able to demonstrate continued safety through innovating in the clinical trial operational delivery space. So we have seen the advent of novel technologies in the clinical trial space are particularly catalyzed by the need for a different approach during the pandemic. So we've seen novel technologies being used across clinical research catalyzed really by the pandemic. And so that could include the opportunity for remote data capture and remote monitoring, tele-visits, the ability to conduct clinical research away from brick-and-mortar sites, particularly around a hybrid space.

So I think there's a real opportunity with these vaccine studies and where we have a high volume of participants engaging in this research, to try and innovate in the clinical trial space and understand how we can conduct clinical trials more efficiently, ensuring that a high volume of participants can engage while we still are able to collect robust endpoint data. And really, technology can facilitate that by making the whole process easy by providing a high user experience. And so of course, with that, as you make clinical trials more efficient, you have the opportunity to collect a wider range of safety data more quickly. So I think that would address the challenge that some of the novel technology in the vaccine space can bring from a safety perspective.

Dr. Turck:
Before we close, Mr. Khan, do you have any final thoughts or takeaways you'd like to share with our audience?

Mr. Khan:
So well, I mean, I think, you know with so many of these significant advancements that this does feel like it's a game changer to think about how targeted mRNA vaccines could be used across a range of therapy areas. We've seen that, you know, they've been applied successfully for COVID-19. That really highlighted the great potential for mRNA vaccines as a novel therapy.

So, you know, though there's been significant success, there are still challenges that need to be addressed for future development, including kind of understanding more about the adjuvant effects, along with the antigen expression. We need to think about how we can improve the stability of mRNA vaccines. And really think about how we manage the safety and some of the particular biological workflows that result from mRNA vaccines, particularly around, escape mutations and breakthrough infections.

So there's still work to do, but certainly a very promising time. And there's a real opportunity to change the way that we treat disease.

Dr. Turck:
Well, with those insights in mind, I want to thank my guest, Mr. Musaddiq Khan, for sharing his thoughts on applications of mRNA therapeutics. Mr. Khan, it was great speaking with you today.

Mr. Khan:
Great being here. Thank you.

Announcer:
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