

**John:** When I was training as a busy physician in the clinic, I understood that if I worked longer hours or I worked harder, I might be able to see more patients every day and in that way, improve more people's wellbeing. But then a pivotal moment came during my training when I realized that if we could discover treatments using research and clinical trials, then that not only would benefit the individual patients who might be enrolled in clinical trials or indeed receive the benefits of a proven therapy as a consequence of clinical trials. But that would then benefit not just the people I directly saw, but everyone on the planet and everyone on the planet for the future.

**Adam:** That's Professor John Rasko. He's a hematologist, a physician, and the head of Cell and Molecular Therapies at Royal Prince Albert Hospital in Sydney, Australia. John is a leading voice in the quest for effective gene therapy, especially when it comes to that crucial stage: the clinical trial.

**John:** Clinical trials are the cornerstone of all modern medicine. It is crucially important that we undertake clinical trials because without evidence, everything else falls away.

**Adam:** Clinical trials are an important step in gene therapy's journey. They are how we demonstrate that therapies are safe and effective enough to warrant giving them to patients. But when you're working with a patient group that's so small, spread out around the world, and trying to treat a disease that doesn't already have a standard of care. There are plenty of challenges.

Welcome to Science Will Win, a miniseries exploring the future of gene therapies, presented by me, Adam Rutherford.

Just a reminder, gene therapy is a promising area but it's investigational in nature for many diseases. There is much research still to be done to better understand the safety and efficacy of these potential therapies. Remember, you should always discuss treatment options with your healthcare provider.

In Episode one, we looked at the basics of gene therapy – and why it matters. And that brings us to where we are today.

**Suneet:** I think the science is really, right now outpacing the policies that we operate our healthcare system by. And we know that these people are living with rare diseases. They don't have time to lose. So how do you bring an entirely new treatment method, a new standard of care that requires a total change to how people can access it, how they can afford it, how do we deliver it? And how do we follow up with those patients?

**Adam:** That's Suneet Varma, Pfizer's global president of rare diseases. And he's asking these questions at a pivotal moment. Because around the world, there are hundreds of ongoing cell and gene therapy clinical trials

With the pace of the science accelerating, today we're taking a deep dive at the development process. And trying to answer the all-important question: What does it take to get a gene therapy approved and out to market?

Clinical trials begin their lives in a lab. In the next stage, they move to preclinical studies with the main goal being to test the action and safety of a potential treatment before beginning to test in humans. Once a therapy has passed these early stages, it then moves to phase one.

**John:** Our first step to demonstrating whether a drug works is a so-called phase one trial wherein we usually don't treat more than a handful of maybe a dozen patients to show whether or not the drug is safe. That's the first and primary goal of a so-called phase one. Then we follow the path through phase one to phase two, and ultimately the phase three studies become the pivotal proof that the drug is not only safe, but also effective in a particular disease that we're testing it. That's based on statistics and based on a complex analysis of the outcomes that were defined at the start of the trial that is then published, peer reviewed and importantly assessed by regulators when applications are made then to market the drug.

**Adam:** And then, at that point, government regulatory authorities can decide to approve a drug, based on the data collected during a clinical trial. The clinical trial process from lab to Phase 3 usually takes around 10 years.

While the process itself is actually fascinating, I also want to make sure we remember that participating in a clinical trial can be a huge decision for patients.

**John:** What each one of these individuals exhibit to me is extraordinary courage because almost invariably, they come with an idea that if they do not benefit, at least they are changing the possibility of the future and what could be more significant for a person suffering from a genetic disease, which they know may well have the possibility of being passed down to future generations. They have a direct connection with those future generations and the disease that they've had to tolerate or suffer throughout their lives.

And so many of the patients who find themselves undergoing a gene therapy in my clinic are there for one reason, they are courageous, but the reason is to make the world a better place.

**Adam:** John Rasko has walked through this decision with patients.

**John:** The consent process is intrinsic and essential because of the implications, especially of gene therapy, because we're talking about a living therapy, a potentially life changing therapy, but let's be clear one that at the current level of technology may present risks. And those risks are sometimes not the kind of risks that people are familiar with to date.

**Adam:** And then, there's the fact that for gene therapy, although this might change in the future, our current understanding is that most patients will likely need to be monitored for 10-15 years to track the long-term safety and durability of the treatment. During that time, it

impacts their everyday lives. There are weekly and then monthly doctor's appointments that can involve various tests, including blood tests, x-rays, and sometimes biopsies. For many patients and their families, the risks and the commitments are worth it.

**Emily:** When my son was diagnosed, my immediate thought was what clinical trial can I get him on and where, and I will move my entire family and my life to do that. The opportunity didn't present itself. And I've had time to reflect over the years about that. And sadly, we've seen a number of clinical trials fail in Duchenne muscular dystrophy. We've seen a number of trials end without positive results in Duchenne muscular dystrophy, we've seen five clinical trials come to an end in recent years. And whilst we have learned an awful lot about the disease from those clinical trials the treatments didn't show efficacy, and this is devastating for families, absolutely devastating. And I think it's our job. And I think it's the job of clinicians and companies to really try and get this point across is that clinical trials are just that. They are experimenting.

**Adam:** That's Emily Crossley. She's the co-founder of Duchenne UK, a charity that raises money and advocates for Duchenne muscular dystrophy. Her oldest son is 14, and he was diagnosed with Duchenne when he was three and a half years old.

Now, Duchenne muscular dystrophy is a rare genetic disease mostly found in young boys that affects the muscles. For people with Duchenne, their bodies don't produce the protein dystrophin. Emily describes it as a coat hanger, a support system for the muscle cells. Dystrophin helps them heal after exercise, or even just daily use. Without it, muscles can degrade.

**Emily:** And for me, the cruelest part of this disease is that in most cases, it doesn't affect the brain. And so boys are trapped in bodies that they know are dying on them, and they know that, and there is nothing they can do. To me, that is one of the cruelest pieces of Duchenne and the fact that it's a relentless downward trajectory of muscle loss. And my son, when he is in his mid-teens in what should be the prime of his physical life will be slowly being paralyzed by this disease.

**Adam:** For Emily, and the parents she works with through Duchenne UK, there's no time to wait. But there are very real barriers to taking part in a trial.

**Emily:** Shortly after my son was diagnosed, Alex, my friend and co-founder, and I discovered that they were turning away clinical trials in the UK because there weren't enough doctors and nurses and physiotherapists and trial coordinators to run the trials. And this was in spite of the fact that we had a real wealth of knowledge in the UK.

**Adam:** And so, Emily and her team at Duchenne UK set up the DMD Hub, to expand clinical trial capacity. They've invested nearly 4 million pounds, and there are now 11 hub sites in the UK, delivering clinical trials for boys with Duchenne.

But sometimes, the challenge isn't just whether or not a hospital can administer gene therapy. There's still a question of eligibility.

**Emily:** I am concerned that we're still very early in the process of gene therapy and there's still so much, we don't know questions like how durable is this treatment? How long will it last in the body before we have to re dose? And this leads on to the next crucial question, which is when you are administering a virus into a human body, you first have to check whether or not that body has antibodies pre-existing to that virus.

**Adam:** What does that mean? When you are naturally exposed to a virus, your body makes antibodies to fight that virus. Because gene therapy is using parts of a virus as the way to deliver this new gene, your body may already have antibodies against that virus. If that is the case, the gene therapy itself may not work.

But there are other considerations to be made when it comes to eligibility, there are very strict and specific criteria for who can participate in trials, depending on age, disease stage, what other drugs they're taking, and what other diseases or disorders they may have.

And so, just getting into a trial can be a huge feat. And while there are success stories, not every trial will lead to a drug.

**Emily:** I think everybody goes into it, must go into it with their eyes open. And in these days of social media, it's becoming more challenging because if a trial comes to an end and the data is not positive, families will find out on social media. That is a devastating way to find out that for the last three years of your life in your eyes has amounted to nothing because the treatment didn't work and it's now going to stop. And many families express to us that they feel the treatment was working. You know, maybe this is placebo effect.

Maybe it was the improved care they were getting because they were going to hospital once a month, once a week. You know, maybe there was something there, but the choice is taken away from them. Then the power is gone. I liken it to being on the Titanic, when your child is diagnosed, you feel like you are on the Titanic and you are sinking to the bottom of the earth. And then you hear about a clinical trial of a potential potentially promising medicine. And there's the lifeboat and you see the lifeboat and you will do anything to get to that lifeboat. And that's how families view clinical trials. You know, they are a lifeboat and a potential lifeline out of the diagnosis of Duchenne. So when that trial ends with negative data, you can see how devastating that is. It's like living the diagnosis all over again.

**Adam:** There are a lot of complications that can make clinical trials challenging for rare diseases. And to learn more, I wanted to talk with someone who has been working through those challenges.

Brenda Cooperstone is the chief development officer for rare disease at Pfizer.

**Brenda:** And what that means is that I have responsibility for the clinical trials that are done for patients with rare disease to look for medicines that will become treatments for them.

**Adam:** Brenda started her career as a pediatric nephrologist, which is basically a kidney specialist for children.

**Brenda:** So pretty much my whole professional life, all I've done is rare disease. And that is very much a passion of mine. I'm very concerned with making sure that patients with rare diseases have access to medicine. And it was actually a pretty easy transition from being a practicing doctor, to working in industry. What it meant was that instead of being able to help one child at a time, I really have the opportunity to help several thousand at a time. And that's really what I want to do and what I'm all about.

**Adam:** We talked to Brenda about the ways that trials for rare diseases differ from a typical clinical trial. The unique hurdles they face. The first is inherent in the diseases themselves: They are rare.

**Brenda:** For common diseases, like heart disease or diabetes. We understand a lot about it because it's been studied and studied extensively. So there's a lot of information out there that tells us what kind of clinical trials we should run, what end points we should measure, what patients are interested in. When you're looking at a rare disease, there's actually very little information out there. We don't know the natural course of that disease because it really hasn't been studied very well.

**Adam:** Then, it comes to finding participants.

**Brenda:** So in a non-rare disease in that phase two first in patient trial, we often will administer it to hundreds of patients. In a gene therapy, rare disease trial, sometimes we'll only put it in two or three or four patients. So it's a vastly different scale. And even for the phase three trial, in a common disease, we're administering it to thousands of patients and in a rare disease, often it's tens of patients, 20, 30, 40, you know, sometimes if the rare disease is a little less rare, we might get up into the hundreds of patients. But it's on a scale that is vastly different from what you would see in a common disease.

**Adam:** Add to that the fact that patients may be spread out across the world, or they may be in a country or city that doesn't have clinical trial facilities.

In the best of cases, gene therapy isn't going to be the right treatment for everyone. But, to the extent that they can be, these challenges are important to overcome.

**Brenda:** I think the issues with equity and healthcare that you see with common diseases are mirrored in rare diseases and maybe increase because the health care and access to healthcare is really in the highly specialized areas, which, if you're poorer or less educated are even more scarce in terms of their availability for you. So issues with regard to equity are amplified.

I think the onus is on those of us who are conducting clinical trials in patients with rare disease and with gene therapy to ensure that we are accessing the right patients and ensuring that our trials are open to patients of all races, of all socioeconomic levels. And that we have the mechanism in place, along with our partners in the academic world to ensure that there is equity in access. That means going to geographies, going to patient communities, ensuring that there is adequate education available across a broad swath of the patient population, so that, everybody understands that clinical trials, as a method of healthcare as a way of accessing healthcare is open to them.

**Adam:** Because rare diseases involve small populations of patients who live all around the world, there's another step in the clinical trial process that's crucial. It's called real world evidence, which is derived from real world data.

**John:** When we talk about the importance of clinical trials on the path to getting approval, it really is towards a trajectory of real world data. And I can't emphasize the importance of vigilant accrual of real world data subsequent to any new drug, but in particular gene therapies because of the technical challenges that they present. And the fact that it really is a new way of delivering medicine.

**Adam:** That's John Rasko again.

Real world data is collected from a variety of sources, but one way that it can be used is to check in and further follow up with patients after they've gone through the clinical trial. While clinical evidence from a trial is seen as the gold standard, this additional layer of data is vital. Gene therapy is expected to be administered just once. And there's still so much to understand about the durability of the effects. But, the hope is that gene therapy will provide benefits to patients for a very long time – if not a lifetime. And because of real world data, we can get a better sense of how gene therapy behaves in patients over time, and that helps the scientists understand how long the effects can last.

But real world data also tells us much more than that. For example: how long gene therapy lasts is also something that health authorities, regulators, insurance companies and health plan providers -- need to know. It's how we determine value for these therapies.

And it doesn't stop with the clinical trials. If a drug is approved, and available to patients, further data is still a vital piece of the puzzle.

**John:** So going forward, it is absolutely essential that individuals who receive approved marketed gene therapies allow at least some of their data with necessary privacy and confidentiality regulations complied with, that they allow their data to be collected at various intervals for many years, hopefully so that we can then develop knowledge about subsets or individuals who may benefit more or who may benefit less or who may need different management

And then it all feeds back on itself because the concept of bench to bedside and back means that ultimately when we do have an approved therapy, we get knowledge about that. We can test things back in the laboratory, back in animal models, perhaps, and then change our phase 1, 2, 3 process to improve those therapies. And indeed that's the way medicine continues to be self-improving and science continues to feed into itself and self-correct as we learn.

**Adam:** Gene therapy is at a pivotal moment. After decades of research, the science is now advancing quickly. But policy is struggling to keep pace.

Simone Boselli is the public affairs director at EURORDIS – that's the European Organization for Rare Diseases. Now, EURORDIS is this huge umbrella organization that includes more than 900 member associations across more than 70 countries. And they're focused on promoting research and development for finding treatments.

**Simone:** We try to strive for better treatments, better care pathways, better social environment for people living with rare diseases. In nutshell, I would say that we work across the lines of different, rare diseases trying to extract what is in common of this, many rare diseases to try to shape an environment.

**Adam:** EURORDIS recently published a study called Rare 2030. They took input from patients, health care providers, and other leaders in the space to make key policy recommendations for the future of rare disease in Europe.

**Simone:** I'd say we are, and I quote one of my favorite basketball player ever, Kobe Bryant when ask at, you know, I believe it was a semi-final or a conference final being two nil up, he said job's not done. And that's where we are. At the moment we are two nil up, but the job is not finished

In many cases, the, primary preoccupation of patients is how do I get the new treatment? Why is it not in my country? And I understand that this is the difficulties in, having quick response, but we can see looking back 20 years, that the changes that we done policies do have at European level have had a profound impact on how some rare diseases have been tackled the attention, the reduction in stigma, the reduction of inequalities on the workplace, but also between countries that have been a result of the advocacy and policy activities that have been done at European level. So yes, we are working possibly for a longer period of time, but we see that we have at least a vision on where we want to be heading.

**Adam:** The landscape looks similar in the United States. While the healthcare system is different, similar challenges remain.

**Erik:** I think it's widely recognized that the United States is a leading, the challenge today is that there's not one simple solution on how to make these more accessible. And that's why I think it's so important that all these different stakeholders and policymakers, you know, are working together to address some barriers that are out there right now in the United States.

**Adam:** That's Erik Paulsen. He's a former congressman and the current chairman of the Institute for Gene Therapies.

And one of the big areas of policy we're going to be focusing on more in this season is value and payment. This is something Erik has seen to be a sticking point in the U.S.

**Erik:** The reality is that with Medicare and Medicaid and federal price reporting requirements being a big part of the healthcare system today, that's where the healthcare system has not caught up with the science. And so the value that gene therapies can bring over the long term is enormous. And so rather than just paying for chronic care treatment of patients where we're spending 85 cents of every dollar today, managing symptoms of chronic illness over a patient's lifetime, there's an ability now to look at one time, potentially long-term durable treatments, and that long lasting effect will greatly reduce and enhance the value and potentially even eliminate in some cases, the need for ongoing treatments and procedures over a patient's lifetime.

And so making sure that our federal systems are set up for value, where there's risk taken by the healthcare providers, or industry, for instance, if there's no benefit to the patient, then that's the risk that those research dollars have gone into. But if there's benefit for the patient, that's where the federal reimbursement system needs to make sure it's reflecting, and paying for that value. And so it's part of the mission of, I think for the Institute for gene therapies is really focusing on educating policymakers and other stakeholders, not only about the potential, but how we can have a more novel reimbursement and regulatory system, so that accessibility to these treatments is going to be realized.

**Adam:** We'll be exploring this landscape at a finer scale in our next episode. But policymakers are just one of many stakeholders that play a vital role in transforming patients' lives through gene therapy treatment. The hope for the future is clear. Here's how Brenda Cooperstone sees it:

**Brenda:** Now I really feel like we're on the edge of a phenomenal, not incremental, but fundamental change in the way that we're going to approach therapies for people with genetic disease. It's amazing that we've really understood some of the genetics behind disease for decades, but have really only worked around the periphery in terms of therapeutics treating symptoms, really trying to address the problem through means that are really not directed at what the problem is, which is a genetic mutation. So the idea, the concept that we can really address the genetic mutation at its heart, what's really causing the disease, not just a symptom, is incredibly inspiring.

**Adam:** Next week on Science Will Win, we're going to be looking at the big policy challenges in Europe and the U.S. And we'll take a look at how advocates, patients, people in the industry, and policymakers are collaborating to overcome them.

## Science Will Win S1E2

We'll cover the policy and regulatory hurdles, why it's so challenging to put a price on these therapies, and the infrastructure needed to efficiently get this medicine into the hands of patients.

Science Will Win is hosted by me, Adam Rutherford.

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See you next time.