How clinical research is engaging with millions of us as ***partners in advancing medicine***

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EDITORIAL DIRECTOR
Jeffrey Zuckerman

DESIGN DIRECTOR
Richard Mooney

COPY EDITOR
Scott Finger

SENIOR CORRESPONDENT
Hannah Thomasy

MARKETING & PROMOTION
Joan Chambers, Lindsey Elliott, Nicole Weiland

This publication, which marks the 20th anniversary of TIME's Apr. 22, 2002 issue, is published by CISCRP (Center for Information and Study on Clinical Research Participation), a first-of-its-kind nonprofit organization dedicated to educating and informing the public, patients, medical/research communities, the media, and policy makers about clinical research and the role each party plays in the process.

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Foreword

Twenty years ago, Time magazine dedicated its April 22, 2002 issue to characterizing and exposing the dangerous and demeaning role of patients in clinical research. The cover image with the attention-grabbing headline "How Medical Testing has Turned Millions of Us into HUMAN GUINEA PIGS" showed a woman in a hospital gown as an experimental test subject in an animal crate: vulnerable, alone, and frightened.

The magazine cover may have been sensationalistic, but the truths in the feature articles both surprised and stung the professional clinical research community. The compassion and professionalism they had brought to their relationships with clinical trial participants was clearly insufficient. A great deal of discussion, debate, and soul-searching ensued in this insular community but there was little to no public response from professionals whose integrity and motives had been questioned.

Most astonishing to me, no one came to the defense of the woman in the cage.

No one sought to correct the image of clinical trial volunteers not as helpless and passive animals in scientific experiments, but as brave ordinary people who willingly give the gift of their participation to help advance medical knowledge that benefits us all. The decision to volunteer is an altruistic act that always carries risk, usually offers no direct personal benefit, yet contributes profoundly to collective knowledge about the nature of disease, its progression, and how better to treat it in the future.

That Time magazine issue struck a major chord in me; I would come to find that it had done so for many others. It was an inflection point marking more rapid adoption of the patient engagement movement. It became the impetus for a unique nonprofit education and advocacy organization—the Center for Information and Study on Clinical Research Participation (CISCRP)—whose mission is to inform and engage patients and the public around the world as partners in clinical research.

This special issue marks the twentieth anniversary of that Time magazine article and shows just how far the patient engagement movement has come since. It recognizes the numerous stakeholders in the clinical research enterprise, and it spotlights new organizations, new functions, guidelines, policies, practices, and solutions that amplify patient voices and needs, improve transparency and disclosure, enrich the clinical trial participation experience, and promote collaboration between patients and the clinical research community. It is remarkable just how much the patient engagement movement has evolved in the past two decades, and it is exciting to envision the next two.

This important anniversary issue was made possible by the work of many individuals. Our hope is that it will be circulated widely and that it will help all patients and the public to see and understand the many ways we can actively and meaningfully engage with the clinical research enterprise today.

Twenty years ago, the clinical research community would say that the patient failed the clinical trial. Today we say that the clinical trial failed the patient—and that is progress well worth celebrating!

Ken Getz
Founder, CISCRP
Executive Director and Professor, Tufts University School of Medicine

From Subject to Partner: The Evolving Relationship Between Patients and Clinical Research

Benjamin Stecher was only 29 when his aunt, a doctor, noticed his hands were shaking. He was referred to a movement specialist who gave him a life-changing diagnosis: Parkinson's.

He tried to go on with his life as usual, returning from his trip home to Toronto and continuing his work at an education company in China. But the disease progressed quickly, and within a few years he decided to return home to Canada. He dedicated himself to researching his disease, since, he'd realized, "there's not a lot of good information for patients out there." What he did find is that there is still no cure, nor any therapies proven to slow disease progression. "I thought that maybe I could make a big difference," he said. "I thought that I could understand the science and I could help influence the course of science."

Today, Stecher is part of a clinical trial testing a new form of deep brain stimulation therapy—and, despite not being a researcher himself, he is helping to shape the direction of Parkinson's disease research by identifying patient priorities for research and treatments and advocating for personalized therapies for this highly variable disease. He speaks at events and conferences across the northern hemisphere, and consults for organizations with such aims as identifying more precise biological indicators of neurodegenerative diseases and potential disease subtypes—which can result in brain dysfunction and death—and analyzing brain data for use in improving therapies for Parkinson's and other brain disorders.

More and more, patients like Stecher are getting involved in research, not just as participants, but as partners. "Patients want a say in how clinical trials are run," said Kate Gillies, director of the Health Care Assessment Programme at the University of Aberdeen. Clinicians, in turn, are recognizing the insights patients bring to the table.

"Clinicians can assume they know what the answer is, but it often takes talking to a patient to make them shift their focus."

Researchers study the symptoms and underlying mechanisms of a disease, but they are not the experts in how people *experience* the disease. Gillies considers a group involved in clinical trials in rheumatology, including disorders like rheumatoid arthritis and lupus, a case in point.

"For years, they'd been doing these trials and the clinicians had been saying, 'we must measure pain, pain is important to patients.' And then they started talking to patients." As it turned out, many patients managed their pain with available painkillers, but said they struggled with fatigue. This group recommended that future studies of rheumatoid arthritis measure fatigue. "Clinicians can assume they know what the answer is," said Gillies, "but it often takes talking to a patient to make them shift their focus."

Empowering patients as partners in clinical research has numerous benefits. Patients can advise researchers on which questions are most important to the people the drug or device is intended to help. Patients know what risks or side effects they would tolerate for the possible benefits of treatment, and how many invasive procedures would be too much. And they can suggest ways to make it easier for others to become involved in clinical trials.

"There's a moral imperative to engage patients," said Kenneth Getz, Executive Director of the Tufts Center for the Study of Drug Development (Tufts CSDD) and founder of the Center for Information and Study on Clinical Research Participation (CISCRP). "But there is also a business imperative."

"There's a moral imperative to engage patients—but there is also a business imperative."

Proponents argue that upfront investments in patient engagement can indeed save both time and money.

"Like in any other industry, it's bad practice to not engage your customer base, and participants are the customer base," said Peter Schaeffer, who leads the Patient Experience Initiative at TransCelerate, an industry consortium dedicated to accelerating the development of new therapies.

A 2016 global study conducted by Tufts CSDD found that in a typical clinical trial, four out of 10 research centers enroll fewer patients than planned, and 11% don't enroll a single patient. And a 2020 global study found that only half of patients screened for non-oncology clinical trials completed them. For oncology clinical trials, less than a quarter of patients screened completed them.

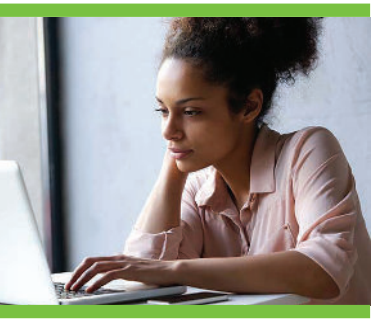
Can patient engagement really help solve these problems? Schaeffer thinks so. "By having conversations with patients and understanding what success looks like for a participant, you can then tailor your trial to meet those needs," he explained. "If you try to tailor your trial to the participant population, you'll have better recruitment—basically, you're able to start your study faster. That reduces cost, obviously. So that's a benefit to the trial sponsor. You'll have better retention as well."

A 2020 study combining published research and interviews across pharmaceutical and research organizations found that creating patient advisory boards and involving patient organizations improved study enrollment, among other impacts. Researchers have also identified specific trials that benefited from patient engagement. In the Prostate Testing for Cancer and Treatment trial, patient input on consent forms and renaming the "watchful waiting" group to "active monitoring" as per patient recommendations increased patient recruitment by more than 40%.

These upfront costs of creating patient-centric initiatives can reap significant dividends. When Getz and researchers at Janssen R&D, Duke University, and Tufts CSDD created a financial model, they saw that a $100,000 investment in patient engagement for trials entering phase 2 or 3 could result in a hundreds-fold return on investment. This held true even when clinical trials' relatively high average failure rates were factored in. Jamie Roberts, one of the study's authors, calls recruitment "probably the single most expensive issue in clinical trials."

"Better planning will lead to faster recruitment, which will lead to faster results, which will lead to bringing drugs or devices to market faster, where they can improve public health," said Roberts. "So, while you may have to spend a bit more up front, you will save more in the long run because you will get to an answer sooner—positive or negative."

In 1988, the HIV/AIDS epidemic drove the activist organization ACT UP to stage a "Seize Control of the FDA" demonstration. Protesters blocked the entrance to the building; some lay on the ground, holding tombstones reading "R.I.P. Killed by the FDA." Their demands were for the FDA to shorten the approval process for potentially lifesaving drugs, improve representation in drug trials, and, because HIV and AIDS at the time meant a nearly certain death, stop using placebos in trials and instead compare a new treatment to other approved or experimental therapies. In many ways, the demonstration was a success: the FDA created policies to allow HIV/AIDS patients increased access to investigational drugs and an HIV/AIDS patient group was created at the FDA.



This would be the FDA's first official patient engagement initiative.

In the years since, patient-driven change has spurred on the research community. More and more organizations are developing tools for patient engagement, funding patient-partnership research, and studying patient engagement itself, figuring out costs and benefits and establishing best practices.

Over the past decade, the Patient-Centered Outcomes Research Institute (PCORI)—authorized through the Affordable Care Act—has funded hundreds of studies to help patients and their doctors make more informed treatment decisions and to identify research priorities for patients and caregivers.

The UK-based National Institute for Health Research (NIHR) provides the Patient Engagement in Clinical Development Service, which offers patient-insight sessions to enable direct dialogue with patients for those companies seeking to understand how patients manage their disease, how to elucidate information about a trial, and which burdens of participating in a trial are and aren't acceptable.

These sessions have changed trial designs. For example, one company asked patients and caregivers to review a protocol for a clinical trial for a therapy for Sjögren's Syndrome, an autoimmune disease. It would have involved multiple lip biopsies, but the feedback led the company to reduce the number of invasive procedures, which encouraged more patients to enroll in and complete the trial. For patients, NIHR's Kim Down said, "the burden of the trial has to be balanced against the experience of living with the disease or the condition."

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Patient organizations are also identifying research priorities. The Cystic Fibrosis Foundation's Community Voice Program uses surveys and focus groups to solicit input from patients and family members on their priorities for research. The Community Voice Program has identified infections as one of the most pressing concerns for people living with cystic fibrosis. As a result of this input, a $100 million Infection Research Initiative was founded in 2018, which will focus on improving infection detection, optimizing current infection treatments, and developing new therapies.

The Food and Drug Administration (FDA), in turn, has hosted dozens of patient listening sessions since 2019 for conditions including celiac disease, lupus, and cystic fibrosis. In these sessions, patients share how their symptoms impact daily life, which should be priorities for treatment, what level of risk they will tolerate, and types of studies in which they would

participate. Vishal Bhatnagar of the FDA's Patient-Focused Drug Development (PFDD) program in oncology, says these sessions "have provided an avenue for inclusion of the patient voice in drug development."

Pharmaceutical companies are also conducting patient advisory boards, in which a small group of patients are invited to provide input on things like protocol feasibility and informed-consent documents. But given the thousands of clinical trials conducted by industry each year, patient advisory boards remain the exception, not the rule. "Of the protocols that will soon be finalized and then put into an active trial, we estimate that less than 15% are including an advisory board," said Getz.

Julie Breneiser was diagnosed with Gorlin Syndrome, a rare genetic disorder, at the age of 12. She is now the Executive Director of the Gorlin Syndrome Alliance and works with pharmaceutical companies and the FDA to push for therapeutic advancements. "The goal of any PFDD or listening session is to teach the FDA about the burdens of the disease," said Breneiser. "You can't speak for someone with a rare disease unless you've really been with them through it and been a part of it."

In October 2021, Breneiser co-moderated an externally-led PFDD for Gorlin Syndrome. "At the end of that day, I felt empowered, exhausted, moved—and relieved. It was a year and a half of work," she said. "We asked people to show what goes on behind closed doors. We put on a good face most of the time, in spite of what's going on inside. People really opened themselves up during this meeting. And that is empowering when you know you're saying it to a regulatory drug authority like the FDA."

Even so, Breneiser wonders about the session's impact. "Are they hearing us? That's still to be determined."

Many patients want to be sure that engagement efforts genuinely involve them in research.

"A lot of patient advisory boards that I've seen are just token boards," said Benjamin Stecher, the Parkinson's research advocate. "They're not empowered to do anything that actually influences the course of the company or the drug that's being developed."

Stecher is currently chairing the patient advisory board at Rune Labs, which he said is a good model for patient centricity. "I really applaud the CEO for allowing me to help guide the company to make sure they have the patient at the center of everything that they're trying to do. Patients are the ones who are going to be using everything that they're making, at the end of the day. If it's not tailored for our needs, then it's going to be pretty useless."

"The patient advisory boards are amazingly powerful," said Getz of CISCRP. When patients weigh in on study protocols, "we ask for their reactions to everything from the schedule and the basic design of the protocol to perhaps the more important issues—Is the study measuring what matters to you? Are there elements of the way the protocol is being communicated to you that you have concerns about?" Any consequent protocol changes are outlined in a follow-up letter to the boards' participants, Getz noted, so they know their input has made a difference.

Shanelle Gabriel, a musician, poet, and lupus advocate, serves on CISCRP's patient advisory board. In this context, she said, she can "support other organizations and pharmaceutical companies in thinking about how to center patients and how to get feedback. That's a really big—and fun—thing that I get to participate in."

"[Clinical] trial staff should mirror the communities researchers want to include. There's a need for diversity in who's doing the research."

As a Black woman in America, Gabriel said, she had concerns about joining a clinical trial, given the troubling history of trials involving people of color. (Indeed, clinical trials in the United States remain overwhelmingly White.) Trial staff should mirror the communities researchers want to include, Gabriel pointed out during a board meeting. "There's a need for diversity in who's doing the research," she said.

Focus groups, advisory boards, and patient-focused drug development sessions go a long way to making trials more patient-centric. Researchers are also working on accommodating patients by making trial designs more flexible and easier to fit into daily life.

Since 2013, CISCRP has been conducting large global surveys of patients and the public to understand their participation preferences and experiences. "There's no single model that resonates most with people," said Annick de Bruin, one of these reports' authors. A personalized approach is essential, "to understand what individual needs and preferences are and adapting your clinical trial to that." De Bruin said these reports help inform trial design by laying out "recruitment, retention, and communication strategies that might resonate most with study volunteers—like what information are patients interested in when they're enrolled in a clinical trial?"

While it is important that clinical trials answer the questions patients care about, patients also decide whether or not to participate based on a trial's obligations, which can include extensive travel, invasive or uncomfortable tests, time-consuming visits, or time away from work and family.

Travel was the biggest burden for the more than 12,000 trial participants CISCRP surveyed. Melvin Mann, a patient advocate and retired US Army Major, recalled a three-year-long trial requiring travel from his home in Atlanta to MD Anderson Cancer Center in Houston every three months. These trips involved not just time and money, but also separation from his wife and grade-school–aged daughter.

Frequency of appointments is another major barrier as well, Breneiser said. She has worked with pharmaceutical companies to tailor their protocols for patients. Breneiser said that on average, people with Gorlin Syndrome have missed 24 days of work or school in the past year for doctors' appointments, treatments, and recoveries. Adding substantially more appointments for clinical trial participation is often not realistic. "Patients have to be able to manage the burdens of the clinical trial along with the burdens of their disease," she said.

Clinical trials can lighten this burden by offering concierge services, including transportation to and from study sites, or even childcare. And the COVID-19 pandemic has spurred a dramatic increase in decentralized clinical trials, where researchers actually bring the trial to the patient.

"Decentralized trials are really changing the paradigm of what clinical research has been in the past, which is where you go to the investigator, who oftentimes happen to be in the large medical centers that are not accessible to people in the rural communities," said Sally Okun, Executive Director of Clinical Trials Transformation Initiative. A McKinsey survey conducted in 2020 found that 89% of pharmaceutical and contract research organizations expected to run a trial with most activities carried out at home, nearly double the percentage a year before.

While some complex procedures may always require visiting specialists at major research centers, blood draws and injections can be performed by doctors, nurses, or pharmacists in the community. Several companies are working to provide solutions, such as the recent partnership between Medable and CVS, which will use CVS pharmacies for recruitment and participation in clinical trials.

In some small trials, it is even possible for the patient never to leave their home. In 2020, researchers at Washington University in St. Louis wanted to find out if fluvoxamine, a drug commonly used to treat obsessive-compulsive disorder and depression, may also help modulate the body's immune system, and prevent symptoms like shortness of breath and decreased oxygen saturation in people with COVID-19.

"Participants were screened via email and phone, and informed-consent documents were signed electronically."

For this trial, nearly all data was collected remotely. Participants were screened via email and phone, and informed-consent documents were signed electronically. The medication and other materials for the study, including a thermometer, oxygen-saturation monitor, and blood-pressure monitor, were sent directly to patients' homes. Patients answered symptom surveys online and were contacted multiple times by phone to address any questions or problems participants were having.

"Fully at-home trials are still rare, but the use of wearables and other at-home monitoring devices in [clinical] trials is increasing."

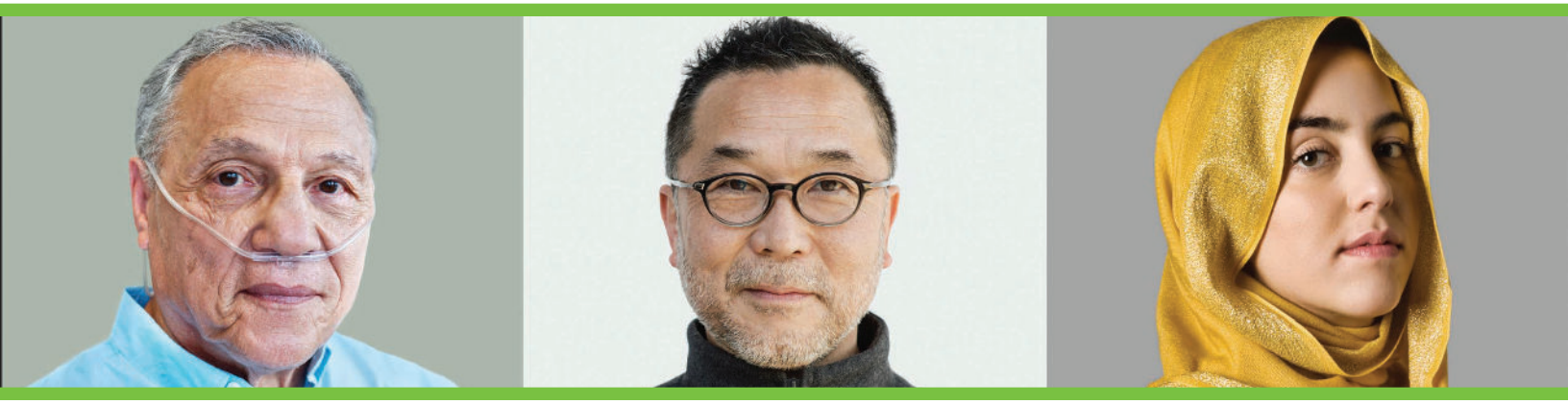
Fully at-home trials are still rare, but the use of wearables and other at-home monitoring devices in trials is increasing. Commercially-available or purpose-built devices can gather data on movement, sleep, heart rate, and oxygen saturation with comparatively little burden to patients. Past and present clinical trials have used these digital endpoints in studies of dozens of conditions, including seizure disorders, Parkinson's disease, insomnia, cystic fibrosis, depression, and more. As a result, patients have a greater sense of freedom and agency even as they participate fully in the clinical trial.

Patients are a crucial part of research, as participants and as designers of the research itself; both roles benefit their communities immensely. "People say that by participating, they are making a difference for the younger generations out there who are struggling," says Breneiser.

"I think I have made a difference in the field," says Stecher. "And I know that I've made a pretty tangible difference in the lives of a lot of scientists and how they do their work. And how they go about actually studying this problem called Parkinson's."

"There's just so much going on today that is putting the patient at the very heart of the clinical research enterprise," says Getz. "It is a golden age for research participation, where the patient is increasingly helping to drive the process."

■ *Hannah Thomasy is a science writer with a PhD in neuroscience. She is based out of Toronto and Seattle.*



Perspectives on the Cover Design

In university 20 years ago, I'd heard about students who had signed up to participate in clinical research studies. Their courage was something I envied and admired. Did they know that they were assisting in scientific advancements that, years later, would result in life-saving and life-enhancing medicines?

During these past 20 years, the clinical trial landscape has changed dramatically and there's been a major push to establish a more diverse clinical trial participant population with greater autonomy in their care, with a louder voice and input into the clinical development process, and with more convenient digital technologies.

These seismic changes signal a renewed period of empowerment and hope for the future. It is these themes that we have tried to capture in the 20th-anniversary publication cover. The cage that was metaphorically restricting the clinical research process has been broken open. The clinical trial participant trapped and bound by a rigid and demanding clinical research process, both physically and mentally, has now broken free, standing confidently, powerfully, and proud. The trial participant, holding a tablet, is connected to and collaborating with researchers through digital channels, embodying the present *and* the future.

Drawing on technology, collaboration, and lessons learned across various sectors will lead to better health experiences and outcomes. As a global, award-winning customer experience agency, our team at RAPP uses behavioral science, data and technology to enable organizations in this diverse health ecosystem to achieve greater potential. We are excited to see what the next 20 years will bring!

Afua Basoah, RAPP
Head of Healthcare Strategy

Special thank you to the RAPP Creative Design Team: *Hiten Bhat, Minas Maroudas, Pawel Rosinski, and Al Mackie.*

CISCRP's core mission is to provide accessible, relevant, useful, high quality educational resources, programs and services that increase awareness and understanding of the clinical research process; recognize and appreciate the unprecedented gift of participation in clinical trials; enhance and enrich the participation experience for patients and their families; and promote engagement and partnership between clinical research professionals, patients, and the public.

CISCRP

One Liberty Square, Suite 1100 ▪ Boston, MA 02109
(617) 725-2750 ▪ 877-MED-HERO (633-4376)

For more information, email CISCRP at info@ciscrp.org or visit www.ciscrp.org