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White Paper

Earning Their Trust:
Challenges and Best Practices in Rare Disease Patient Recruitment

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Introduction

According to the 2025 edition of Citeline's Annual Clinical Trials Roundup, after a decline between 2021 and 2023, rare disease Phase I–III clinical trial initiations are once again on the upswing, accounting for 30% of total trial activity in 2024.[1] Rare diseases, as classified by Citeline's Trialtrove solution, are those with a prevalence of one in 2,000 people in the EU, or affecting fewer than 200,000 people in the US (equivalent to around one in 1,600 people).[1]

Citeline's Pharma R&D Annual Review 2025 notes one in five drugs entering the pipeline during 2024 was targeted against one or more rare diseases,[2] and the Citeline article "Rare Disease R&D: Continued Growth Amid Challenges" states 52% of the novel drugs approved by the FDA in 2024 were for treating rare diseases.[3] Drugs in development against rare diseases in 2024 hit 7,721, up 7.4%, accounting for 32.3% of the pipeline — almost a third, and up from 31.5% the previous year.[2]

This strong R&D trend is expected to carry through at least the coming year. "In 2026, I'm confident that the number of clinical trials for rare diseases will continue to increase," says Wes Michael, President and Founder, Rare Patient Voice. "Orphan drugs are now exempt from several negative provisions of the [US] Inflation Reduction Act, and many expect the FDA to be more favorable in regulating rare disease drugs."[4]

As rare disease research grows, so too does the need for patients to participate in the resulting rare disease clinical trials. Therein lies the challenge. By definition, each rare disease affects a limited number of patients, making the pool of potential participants quite small. And finding candidates within that pool is only half the battle. Rare disease patient recruitment also faces obstacles such as delays in diagnoses, lack of awareness and trust, and difficulties in balancing participation with the day-to-day challenges of living with a rare disease.

Interest there, but patients unaware

Rare disease patients do not lack interest in clinical trial participation. In a 2020 study by the National Organization for Rare Disorders (NORD), 88% of the 1,108 respondents living with a rare disease said they would consider using an investigational treatment. Yet only 16% reported already having participated in a clinical trial.[5]

A 2025 Rare Patient Voice survey of 1,147 patients and caregivers in the US found that 57% were only "somewhat aware" of clinical trials. Out of all respondents, 68% had never participated in a clinical trial primarily because they did not know a trial was available or they did not qualify because their medical history is too complex. And 28% said they would like to hear about clinical trial options from their healthcare providers.[6]

Sponsors should take note of the gap between willingness to participate and lack of information about clinical trials. Making information more accessible — particularly to a trusted resource like their healthcare providers (HCPs) — could help smooth the path to rare disease patient engagement and recruitment.

Delayed diagnosis hits recruitment hard

One of the toughest aspects of rare disease is how long it takes for patients to be diagnosed correctly. According to the 2020 NORD study, 28% of rare disease patient respondents said it took seven years or more for them to receive a correct diagnosis, and 38% of rare disease patient respondents reported receiving at least one misdiagnosis while on their diagnostic journey.[5]

"Patients on average see five to seven doctors to get their actual true diagnosis, and it'll take them at least five to seven years," says Jenifer Waldrop, Executive Director, Rare Disease Diversity Coalition (RDDC). "It's part of the difficulty in recruiting patients for rare diseases because for you to recruit them, they have to be diagnosed. You can't just have all of these symptoms with no diagnosis."

Harsha Rajasimha, Founder and Executive Chair of Indo US Organization for Rare Diseases, agrees diagnostic delays and misdiagnoses can be roadblocks in rare disease clinical trials. "That happens in rare disease if there is no well-defined biomarker, if it's a single gene mutation, and even in a single gene, the mutation could be in different parts of the gene that could manifest differently in different patients. So, heterogeneity may happen."

In these cases, he says, prior existence of patient registries and natural history studies could be helpful. Natural history studies are preplanned observational studies intended to track the course of a rare disease with the purpose of identifying demographic, genetic, environmental, and other variables that correlate with the disease's development and outcomes.[7]

"When those exist, it becomes so much easier to enroll from the natural history study database of well-characterized patients. Still, there may be several patients who may not be in the natural history study yet, and they need to be better characterized. That adds to the complexity of patient recruitment," Rajasimha says.

A 2024 study RDDC conducted with NORD notes the increasing number of innovative rare disease therapies with narrow treatment windows, meaning any delay in diagnosis can exclude rare disease patients from participating in — and potentially benefiting from — clinical trials.[8]

Waldrop says the study findings indicated "patients were not necessarily being asked to participate in clinical trials. Plus, patients were having challenges to participate in the trials themselves, given the construct and the way that the trials were designed."

> "I am finding that more sponsors are including patient advocacy groups and patients in their trial design, which is fantastic."
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> **Jenifer Waldrop**
> Executive Director, Rare Disease Diversity Coalition (RDDC)

More trial codesign involvement

Historically, Waldrop says, some aspects of trial design have not consistently reflected the daily patient realities. For instance, when sponsors plan trials, they often neglect to consider that the sites they choose may not be accessible to the patients they are trying to recruit, or that participants may need assistance with child or elder care. "Even just the paperwork, the language that's being used … it feels very lab-oriented, and that can be daunting," she says.

"But I am finding that more sponsors are including patient advocacy groups and patients in their trial design, which is fantastic," she adds.

Rajasimha says sponsors need to consider the patients' problems and design trials for feasibility and patient burden. "The FDA offers these patient listening sessions which are open to the public. So, if a particular disease's patient communities are speaking, listen to them and

understand what their problems and challenges are, and design protocols that take those into consideration so patients feel like they're being cared for."

Expanding eligibility criteria can also help. "Sometimes the inclusion/exclusion criteria are so narrowly defined that we automatically exclude a lot of patients," Rajasimha says.

Mike Graglia is Founder and CEO of the patient advocacy organization CURESYNGAP1, which focuses on accelerating research for rare genetic SYNGAP1-related disorders. He says the parents of children with these SYNGAP1 disorders are managing a host of symptoms such as seizures, disrupted sleep, intellectual disability and autism, low motility, and severe aggression.

"These parents are on a hair trigger, constantly trying to make sure things don't fall apart, and they're worried about going outside, much less going to a clinical trial. So, when someone calls us and says, 'Hey, there's this experimental therapy that we want to throw into your precious child whom you've spent your whole life defending, and would you please get on a plane and go to be in this trial?' we're going to understandably be hesistant to say the least. I think building trust and convincing the caregiver that you actually understand their needs is a huge barrier."

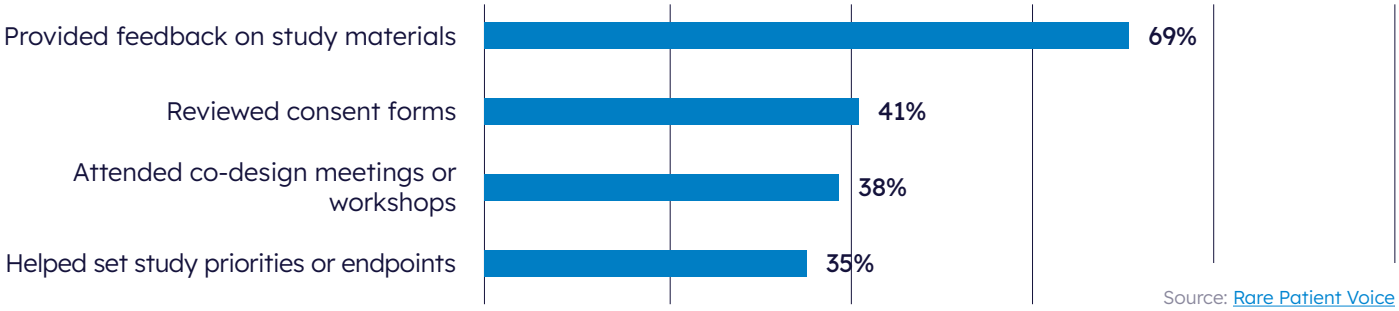
Once they know they can assist with clinical trial design, many patients are willing to lend a hand. In a 2025 study by Rare Patient Voice involving 2,156 US patients, 68% of those surveyed were not aware patients can be involved in designing clinical trials. Nearly all the respondents (97%) believed it was at least moderately important for patients to be involved in clinical trial design.[9] When asked if they would be interested in being involved in the design of a clinical trial in the future, 82% of respondents said yes,[9] and 84% said a clear explanation of the process would encourage them to participate (Figure 1).

Figure 1. What would encourage you to participate in codesign activities?

Source: Rare Patient Voice

Of the 4% of respondents who were involved in clinical trial codesign,[9] just over two-thirds provided feedback on study materials, while just over a third helped set study priorities or endpoints (Figure 2).

Figure 2. How were you involved in the codesign process?



Source: Rare Patient Voice

Given these results, involving rare disease patients in clinical trial design appears to be an excellent way to gain patient awareness and trust, and they will also become more educated on the clinical trial process. This likely will make them more open to clinical trial participation when the opportunity arises.

Graglia notes CURESYNGAP1 is working with a biotech company developing a therapy for SYNGAP1-related disorders and has met with its staff to discuss clinical trial design.

"We put their C-suite in a room with our parents for focus groups. And we've told them what we need. Our parents need someone to book the tickets for them. They need someone to cover the babysitting when they're gone. They need an extra day when they get there for all the drugs they put in their kids to make travel even possible … to wash out before you treat them. It's not that our parents are needy or precious. It's that our parents are white-knuckling it through every day and you're asking them to do something big and complex. There needs to be adequate support there."

> "Building trust and convincing the caregiver that you actually understand their needs is a huge barrier."

Mike Graglia
Founder and CEO, CURESYNGAP1

Building community image

Rajasimha emphasizes the importance of relationship building in rare disease patient recruitment. "Rare disease patient communities are tight-knit, and sometimes when pharmaceutical companies approach them not in the right spirit, with trust and transparency, the rare communities can see that. And because they are so involved and engaged compared to general common disease categories, they become less willing to engage. It's trust and transparency that will become critical in recruiting patients with rare diseases."

He recommends building relationships with rare disease communities and patient advocacy groups well in advance of finalizing the trial protocol. "One or two years before they are ready to start the clinical trial, the sponsor should start building relationships with these patient advocacy groups. … It's important to engage, educate, and get educated by the patients and listening to them. That's critical in rare disease research."

Waldrop notes that recruiting rare disease patients from underserved populations presents special challenges — trust being chief among them. "You have these headwinds that they're not willing to participate because of previous generations' mistrust that's continued to resonate in their community," she says.

Sponsors need to have self-awareness around how their organization is viewed within these communities, Waldrop says. "There are some sponsors I have spoken with that recognize they have not done a great job in creating trust within these communities. They are reviewing how they build trust with communities and are acknowledging the gaps by investing in local partnerships that are close to them. The Rare Disease Diversity Coalition is made up of a variety of patient groups, and you can bet those groups are coming from a diverse population."

Waldrop also emphasizes the importance of sponsors "showing that they're there for the long haul. We do want them to continue while they are recruiting to provide ongoing information and education, because you may not qualify for that trial, but you may qualify for a future trial. You want to know if that sponsor is just going to be what I call 'stick them and leave them,' if they're going to be in that community for that short amount of time and then leave. Community partners can tell when engagement is episodic rather than sustained; multiyear commitments and ongoing education build credibility. If they continue to share how they really do care about the greater health of the community, then it provides a level of street cred and brand for them as a sponsor."

Overall, Graglia says, trust and education are key aspects of recruiting any rare disease patients for clinical trials. “One is getting the families to trust you and listen to you and take this opportunity seriously.

“We’ve worked so hard for so long advancing the science that I wonder if we’ve forgotten to bring the intended audience along to the point where they can even participate. Some people are just going to be like, ‘This is exciting, let’s do it.’ Other people are going to say, ‘Wait, I need to understand, and I don’t think I do.’

“It’s acknowledging that a rare disease by definition hits all levels of society. So, you need to target communications across all levels of education, and those need to all be sitting on a website somewhere where they can get them.

“Also, if you’re a sponsor working on a rare disease, … it probably shouldn’t be your medical affairs person, a doctor or Ph.D, talking to the patient. That person’s intimidating. It should be a patient that you have trained up with your slides, then the medical affairs person can be on the call as well. But I think at the end of the day you have to use the people who have the trust of the community to talk to the community.”

Patient retention requires flexibility

Rajasimha notes the size of the eligible population for rare disease clinical trials “may be very small. If it’s a rare or ultra-rare disease and they are also geographically dispersed, even the so-called good protocols can take disproportionately longer and cost more to enroll on a per-patient level.”

When enrolling in such small populations, every patient becomes precious, Rajasimha says. “In very small population studies, biostatistics need to be tailored to estimate the sample size. The plan will then become capturing a lot of data from a small group of patients. Hence, every patient and every data point during the clinical trial process becomes that much more important to ensure it’s accurately captured.”

Waldrop says there is often a gap between what the site is willing to do to retain a patient and the level of flexibility the sponsor wants applied to retention. She says she has heard stories about people leaving trials because “they’ve had a bad day or they find that coming into the trial is more exhausting than they’re finding it’s worth.”

While a lot of the stressors on patients may be beyond the site’s control, Waldrop notes they still have to take them into account. “The question becomes, ‘How flexible is the trial site in terms of allowing for some of that?’ Because the person may say, ‘I’m out of this, I don’t want to do this anymore. I didn’t feel like I was respected, I’m burnt out.’ And the trial site is like, ‘Well, OK, the person said no. And I’m not going to go and chase them and bring them down to this. I’m not going to take the time to do that.’ Meanwhile, the sponsors know that there’s got to be a level of flexibility. There’s the philosophy, and then there’s the real practice. So there has to be alignment and realities in there, too.

“With retention, we have to be a little bit more flexible if we really want these studies to follow through because it’s so hard to recruit people and then to retain them, and then these people leave for one reason or another. So I think there are lots of opportunities in terms of retaining folks. It’s very much like in a business setting. Why do some people leave? They leave because of people, they leave because of their managers.”

Waldrop says retention is even more critical for rare disease trials because of the small number of patients likely to participate. “The information that we get from those very few patients in this rare disease community holds so much more weight than when we do chronic diseases.”

> “Every patient and every data point during the clinical trial process becomes that much more important…”

Harsha Rajasimha
Founder and Executive Chair of Indo US Organization for Rare Diseases

Decentralized trials not always welcome

There are times when protocols are what Rajasimha refers to as "overbuilt," meaning they require a number of visits or procedures that proves burdensome to the patients. He says sponsors may be looking to capture as much data as possible, even when the study doesn't specifically require it, just to be prepared if regulatory agencies such as the US Food and Drug Administration (FDA) ask for it. "Adding too many procedures, too many blood draws or other 'just in case' endpoints can make the protocols overbearing on the patients, and that may discourage enrollment, protocol adherence, and deviations."

He says sponsors should look at decentralized and hybrid clinical trial elements, which can make it less burdensome on the patient population. "For example, wherever travel can be reduced or replaced with tele-visits and video visits. Reducing the number of blood draws or local labs and home health, remote monitoring and data capture to reduce travel burden can be huge."

Waldrop shares a different view on decentralized trials. She says it's a great idea on paper, but it may not translate to certain communities. "Some populations because of their headwinds or because of their culture, they don't want people coming to their home, if they're doing it through their home as opposed to a decentralized clinical trial at a local pharmacy. But … some people just feel like, 'I don't want my treatments in my home. My home is my oasis.' This is probably true for almost any population, but maybe more so for certain folks that are probably not as embedded in the US culture."

Lack of internet access could be another barrier for decentralized trials if the person visiting the home needs internet access and it is not available, Waldrop says. "Then there's always the language barrier whenever it comes to any kind of paperwork and what have you," she adds. "Health literacy is always an underlying theme for when we talk about diversity of patients when it comes to clinical trials."

Difficulty with the technology involved is another reason patients may balk at decentralized trials. According to the 2025 Perceptions & Insights study by the Center for Information and Study on Clinical Research Participation (CISCRP), 21% of respondents who had participated in a clinical trial and found the experience at least somewhat disruptive cited having to use technology such as a smartphone or tablet as a reason for the disruption.[10] While this study did not focus specifically on rare disease patients, it is still evidence that technology may be a stumbling block for rare disease patients considering decentralized trial participation.

The role of AI in rare disease trials

Waldrop notes that artificial intelligence (AI) has been around for a long time, but it has garnered a lot more attention in the past several years due to globalization and advances in the technology.

"When I think about AI and I think about the rare disease community, I think about the delays in diagnosis," she says. "I see AI playing an instrumental role in helping us hopefully shrink up that odyssey and that time frame. If you can use AI to identify those patients and not have them sitting in the undiagnosed area, then you'll have a richer amount of folks that may be qualified to be in clinical trials in the rare disease community. So, AI from a diagnosis perspective can help in the clinical trials perspective."

In addition to cost and time savings, Rajasimha says he believes AI can be a great help in rare disease patient recruitment by improving patient centricity. "It reduces the human burden of doing all the busy work so the humans can focus on making decisions on what actions to take."

There are challenges with using AI, Waldrop says, specifically because of the volume of rare diseases and their specific symptoms and characteristics. She uses breast cancer as an example. "If you're talking about breast cancer as a whole, that's not a rare disease, but there are certain varieties of breast cancers that are rare and therefore fall under the rare disease category. … So when you're trying to do a clinical trial and you're trying to target that specific disease and that particular variant in there, that's where it becomes a little bit trickier. And we haven't mastered that yet."

Another challenge is the potential introduction of bias. "The people that are creating these algorithms, machine learning, and that type of coding, essentially they have their own biases in there," Waldrop says. "So then, the information is only going to be so accurate. We do need to do a better job from a talent perspective, ensuring those that are in the space are doing it in a more holistic, inclusive way.

"Over time I do see it probably becoming better and better, which it has. We can already see that in our lifetime. And it does impact the clinical trial space as a whole."

Rajasimha notes that AI needs a strong foundation and seamless integration to operate at its fullest potential. "Some people jumping on the AI bandwagon are trying to implement AI on top of whatever they have been doing for the last 10 or 20 years. That's a dangerous precedent, in my opinion," he says. "We should have a strong digital infrastructure to support AI. You can't put AI on 10 different disconnected tools, one focused only on patient recruitment, one only focused on data management, one on patient engagement and retention, and so on. There needs to be a workflow of engaging patients from the very beginning until the study close out and even beyond, returning results back to them and continuing to monitor them for long-term safety. This is a long-term engagement, and hence it needs to stand on a unified infrastructure built on AI-native technology."

Waldrop says it is important that sponsors are transparent about use of AI in their clinical trials so as not to engender mistrust among participants. "Are sponsors willing to share with the communities? 'I am using AI for some of this work, I'm willing to share with you where I use AI, what the role of AI is in the science that we're doing, in the research that we're doing.' It depends on culturally how transparent these researchers are when it comes to clinical trials.

"For those that have some concerns, I think the question is, 'What concerns might they have?' Part of it is their own data. So how do we assure them that the data we are collecting is locked down, that their information is not going to be sent out? Is that one of their concerns? Maybe just finding out if they are sensing that some of their potential participants have concerns with AI.

"But then they need to be willing to communicate with them why they're using AI, how they plan to use AI. And make sure patients know that their data is going to be protected along the way, that they have these stopgap measures and all the stuff the security folks in those biotech pharma companies often do. At the end of the day it's for the sake of the science, so reassure them … that we're doing this together."

How can AI improve rare diseases care coordination with and without diagnosis?

Some ways AI can be used include:

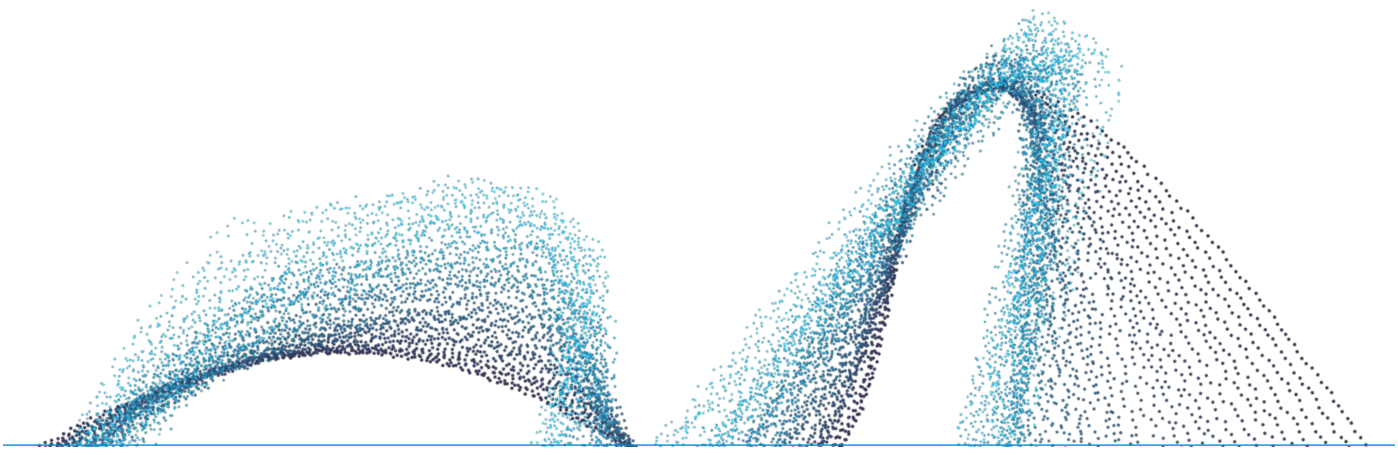
Drug discovery, development, and repurposing
Generative models can speed up drug discovery and development by predicting potential drug candidates and their interactions with disease-specific molecular targets, thus reducing the time and cost of experimental screening. In addition, these models can identify existing drugs that could be repurposed for rare diseases by simulating their effects on relevant biological pathways and suggesting modifications to boost efficacy.

Clinical trials access, matching, and modeling
Large language models (LLMs) can predict the most suitable clinical trials based on individual genetic and clinical profiles, which can enhance patient recruitment and participation. Also, these models can simulate various trial scenarios to optimize study designs and predict outcomes, ensuring more efficient and effective trials.

Public health interventions
Generative models can be used to predict the spread and impact of diseases within populations, enabling more targeted and efficient resource allocation. LLMs can also simulate the potential outcomes of different intervention strategies to help support the development of effective policies and programs tailored to the needs of rare disease communities.

Care coordination models
AI can help evaluate the effectiveness of different models of rare disease care coordination based on the taxonomy of care coordination dimensions and by taking into account the phenotypic profiles of the patients rather than relying solely on an existing diagnosis.

Source: Rare



References:

[1]Fisher S and Chen H (2025) The Annual Clinical Trials Roundup 2025 Edition: Innovation, Regulation, and Preservation. Citeline. Available from https://www.citeline.com/en/resources/the-annual-clinical-trials-roundup-2025 [Accessed Jan. 13, 2026]

[2]Lloyd I (2025) Pharma R&D Annual Review 2025. Citeline. Available from https://www.citeline.com/rd25#review [Accessed Jan. 13, 2026]

[3]Citeline (2025) Rare Disease R&D: Continued Growth Amid Challenges. Available from https://www.citeline.com/en/resources/rare-disease-r-and-d [Accessed Jan. 22, 2026]

[4]Grabenstein D (2026) An Alphabet Soup of 2026 Predictions: GLP-1s, ICH, GCP, CAR-T, AI & More. Citeline. Available from https://www.citeline.com/en/resources/2026-pharma-predictions [Accessed Jan. 14, 2026]

[5]National Organization for Rare Disorders (2020) Barriers to Rare Disease Diagnosis, Care and Treatment in the US: A 30-Year Comparative Analysis. Available from https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf [Accessed Jan. 21, 2026]

[6]Mullen L (2025) Overcoming Reach and Recruitment Challenges to Engage Rare Disease Patients in Clinical Trials. Patients as Partners in Clinical Research. The Conference Forum. Available from https://theconferenceforum.org/editorial/overcoming-challenges-of-reach-and-recruitment-to-engage-rare-disease-patients-in-clinical-trials [Accessed Jan. 13, 2026]

[7]Reissue of RFA-FD-22-001 - Efficient and Innovative Natural History Studies Addressing Unmet Needs in Rare Diseases (R01 Clinical Trials Optional) (2025) Department of Health and Human Services. Available from https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-25-017.html [Accessed Feb. 9, 2026]

[8]Rare Disease Diversity Coalition and National Organization for Rare Disorders (2024) Inequities in the Rare Disease Community: The Voices of Diverse Patients and Caregivers. Available from https://www.rarediseasediversity.org/hubfs/RDDC/Inequities%20In%20The%20Rare%20Disease%20Community%20Survey.pdf?hsLang=en [Accessed Jan. 21, 2026]

[9]Rare Patient Voice (2025) Patient Insights on Co-Design in Clinical Trials. Available from https://rarepatientvoice.com/wp-content/uploads/2025/06/Patients-and-Co-Design-in-Clinical-Trials.pdf [Accessed Jan. 23, 2026]

[10]Center for Information and Study on Clinical Research Participation (CISCRP) (2025) Perceptions & Insights Study 2025. Available from https://www.ciscrp.org/professional-services/perceptions-and-insights-studies [Accessed Jan. 30, 2026]

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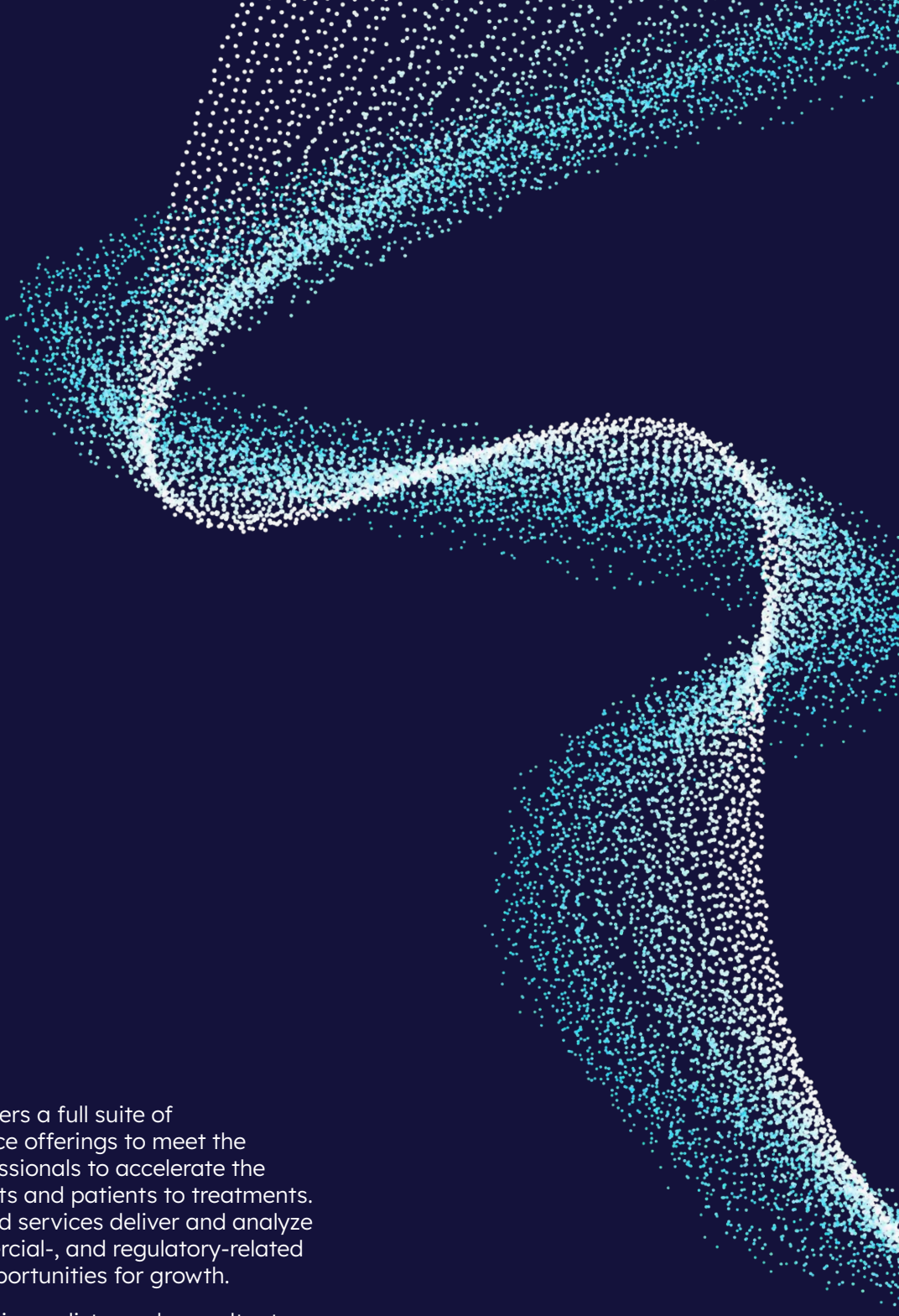

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