Rare Expertise

WHITE PAPER

Nothing About Us Without Us:

The Imperative for Patient and Caregiver Input in Clinical Trial Design

How Engaging Patients and Caregivers as Partners — Not Subjects — Transforms Clinical Development Outcomes in Rare Diseases

A Rare Expertise White Paper

For rare disease marketing and medical affairs professionals

rareexpertise.com

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SECTION 01

Executive Summary

The phrase "nothing about us without us" has long been a rallying cry in disability rights and patient advocacy. In rare disease clinical development, it has become an operational imperative. As rare disease clinical trials grow more numerous and more competitive, the evidence is clear: trials designed with meaningful patient and caregiver input outperform those designed without it — in enrollment speed, retention rates, endpoint relevance, regulatory success, and ultimately, in their ability to deliver therapies that make a real difference in patients' lives.

This white paper examines why patient and caregiver engagement in clinical trial design is not merely a best practice but a strategic necessity for rare disease drug development. It explores the unique challenges that make rare disease trials especially dependent on patient input, the specific stages of trial design where patient and caregiver perspectives have the greatest impact, the growing regulatory mandate for patient-focused drug development, and the practical approaches that leading organizations are using to integrate patient voices into their clinical programs.

4x
faster recruitment
TRIALS DESIGNED WITH PATIENT INPUT

81%
screened but ineligible
RARE DISEASE TRIAL PARTICIPANTS

1 in 4
trials terminated
DUE TO LOW PATIENT ACCRUAL

The evidence shows that rare disease trials designed with patient input recruit up to four times faster, achieve higher retention, generate more clinically meaningful endpoints, and build the community trust that is essential for long-term commercial success. For marketing and medical affairs professionals working in rare diseases, understanding this landscape is essential — because the decisions made at the clinical trial design stage reverberate through every subsequent phase of commercialization.

81%

of patients screened for rare disease trials are *not eligible* — and more than half of those who are fail to be randomized.

TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

SECTION 02

Why Rare Disease Trials Demand Patient Partnership

Clinical trials in rare diseases face a set of challenges that are qualitatively different from those in larger therapeutic areas. These challenges make patient and caregiver engagement not just valuable but indispensable.

Small Populations, High Stakes

The most fundamental challenge is arithmetic: rare disease patient populations are small, geographically dispersed, and often heterogeneous in their disease presentation. Every patient who can be enrolled matters enormously, and every patient who drops out represents a disproportionate loss. Research from the Tufts Center for the Study of Drug Development indicates that 81% of patients screened for rare disease trials are not eligible, and more than half of those who are fail to be randomized. GlobalData research has found that more than one in four rare disease clinical trials terminate due to low patient accrual.

> ● CRITICAL REALITY
>
> **In this environment, trial designs that patients find burdensome, endpoints that do not reflect their lived experience, or visit schedules that are incompatible with their daily realities are not merely inconvenient — they are existential threats to the trial's success. Patients and caregivers are the only people who can identify these obstacles before they derail a study.**

Patients and Caregivers as Disease Experts

In rare disease, patients and caregivers possess a depth of knowledge about their condition that is often unmatched by the physicians treating them. Many rare diseases have no established centers of excellence, limited published literature, and few clinicians with deep experience. Patients who have lived with a condition for years — managing its symptoms, navigating its unpredictability, and observing its progression in themselves or their children — have accumulated an understanding of the disease's impact that no amount of chart review can replicate.

This expertise is particularly critical for identifying the outcomes that matter most. Clinical researchers may focus on biomarkers or functional assessments that, while scientifically defensible, may not capture the changes in daily life that patients and families consider most meaningful. A parent caring for a child with a neurodegenerative condition may prize small improvements in communication or comfort that standard clinical scales completely miss. A patient with a rare metabolic disorder may value reduced fatigue during daily activities more than changes in laboratory values.

> *Patients and their families are experts in their disease and their experiences. Because of this, it is important that we not assume what the experience is but rather directly ask about it. When we design clinical trials, we want to make sure that we are measuring the impact of an intervention on something that matters to the patient and their loved ones.*
>
> Dr. Jennifer Vermilion, Rare Diseases Clinical Research Network

The Caregiver as a Distinct and Essential Voice

In many rare diseases — particularly those affecting children or individuals with cognitive or communicative impairments — caregivers are not merely support figures. They are primary observers of disease progression, managers of complex care regimens, and often the decision-makers about clinical trial participation. Research published in *Applied Clinical Trials Online* highlights two critical roles caregivers play: a facilitative role (managing medication adherence, coordinating visits, and maintaining overall wellness) and an observational role (detecting early warning signs that neither physicians nor patients themselves may recognize or report).

Caregiver perspectives are particularly valuable in assessing treatment response. Standard patient-reported outcome measures may be inaccessible to patients who cannot self-report due to age, cognitive status, or disease severity. Caregiver-reported outcomes and caregiver perception of change assessments offer rigorous, complementary data that can capture nuances invisible to traditional clinical endpoints. A methodology of Patient and Caregiver Perception of Change Assessments — utilizing video interviews conducted before, during, and after clinical trials — has been developed specifically to fill this gap in rare disease research.

PATIENT VOICE

"Caregivers can make or break participation in a clinical trial. We need to think about the whole family when designing trials that are both scientifically sound and ethically responsible." — Dr. Heather Lau, Yale University

The Trust Equation

Rare disease communities are small and tightly connected. News about a clinical trial — positive or negative — travels fast through advocacy networks, social media groups, and patient conferences. A trial that is perceived as burdensome, disrespectful of patients' time, or disconnected from the outcomes families care about will quickly develop a reputation that impairs not only current enrollment but future trials in the same disease. Conversely, sponsors that genuinely engage patients and caregivers in trial design build a reservoir of community trust that accelerates every subsequent stage of development and commercialization.

Patients and their families are experts in their disease and their experiences. When we design clinical trials, we want to make sure that we are measuring the impact of an intervention on ***something that matters to the patient and their loved ones.***

DR. JENNIFER VERMILION, RARE DISEASES CLINICAL RESEARCH NETWORK

SECTION 03

Where Patient and Caregiver Input Has the Greatest Impact

Patient and caregiver engagement can and should span the entire arc of clinical development. However, research and industry experience have identified several stages where this input has particularly high leverage.

Endpoint Selection and Outcome Measures

Perhaps the single most consequential area where patient input transforms trial design is in the selection of endpoints and outcome measures. Rare disease trials face a well-documented problem: for most rare diseases, there are no previously treated populations, clinical endpoints are poorly defined, and validated disease-specific outcome measures are scarce. The traditional model of evaluating treatments based primarily on standard outcome measures has struggled in its application to rare disease.

Patient and caregiver input helps identify the symptoms considered most burdensome, the functional domains with the greatest unmet need, and the threshold of improvement that would be considered clinically meaningful from the patient's perspective. This is not a matter of sentiment — it has direct regulatory implications. The FDA's Patient-Focused Drug Development guidance series now provides explicit direction for incorporating patient experience data into regulatory submissions, and the agency "strongly encourages" sponsors to incorporate patient and caregiver perspectives throughout the drug development process.

> KEY INSIGHT
>
> Survey-based research with patients and families should specifically include questions about which symptoms are most burdensome and where patients experience the greatest unmet need. Given the heterogeneity of symptoms in rare diseases, treatment response may also be heterogeneous, and patient input can help trial designers anticipate this variability and build it into endpoint strategies.

Protocol Design and Visit Burden

Study requirements that appear routine to a protocol writer may have profoundly burdensome implications for rare disease patients whose daily lives are already complex and challenging. There is ample evidence that living with a rare disease deeply impacts individuals and families financially, physically, and psychologically — making it difficult to absorb the incremental burdens imposed by clinical trial participation.

Patient advisory workshops and community advisory boards have proven effective at identifying these burden points before they are locked into a protocol. When Dyne Therapeutics convened panels of individuals living with Duchenne muscular dystrophy and myotonic dystrophy type 1 to inform their DELIVER and ACHIEVE clinical trials, the feedback led to concrete changes: refined inclusion and exclusion criteria, redesigned clinic visit schedules, implementation of a travel support program for long-distance and cross-border participation, introduction of home visits where feasible, allowance for adequate rest before assessments, and development of age-appropriate communication materials.

The issues participants identified as most important were access to the trial, perception of benefit and risk, flexibility of participation, clear communication from the sponsor, availability of information from trusted sources, and the enrollment process itself. These are practical, solvable concerns — but they can only be identified by asking the people who will actually live them.

Eligibility Criteria

Eligibility criteria present a particularly high-stakes area for patient input. In rare disease trials, overly restrictive criteria can exclude patients who desperately need treatment and who represent a substantial proportion of the already-small eligible population. Clinical trial inclusion and exclusion criteria are subsequently mirrored in payer prior authorization requirements, meaning that the boundaries drawn during trial design directly determine which patients will have access to the therapy after approval.

Patients and advocacy organizations can provide critical feedback on whether proposed criteria reflect the real-world population, whether age cutoffs are appropriate, and whether certain exclusions may systematically disadvantage patients who are most affected by the disease. This is not a request to lower scientific standards — it is a recognition that criteria designed without knowledge of the patient population may inadvertently exclude the very individuals the therapy is intended to help.

Recruitment Strategy and Communication

Advocacy organizations are often the single most effective channel for clinical trial recruitment in rare diseases. Research consistently shows that patient advocacy groups produce a high proportion of enrolled patients — in some cases more than clinical trial sites themselves. Engaging advocacy organizations early in trial design — not just at the recruitment stage — allows sponsors to align their protocol with the community's concerns, build trust before enrollment opens, and leverage advocacy networks for awareness and referral.

Communication materials and informed consent documents also benefit enormously from patient and caregiver review. Research with patients with idiopathic pulmonary fibrosis found that some participants found trial information confusing and trial processes frustrating. Materials reviewed and refined by patients and caregivers are more likely to be understood, trusted, and acted upon. This is particularly important in pediatric rare diseases, where caregivers are making participation decisions on behalf of their children and need information that addresses their specific concerns and questions.

Decentralized and Hybrid Trial Design

The growing adoption of decentralized clinical trial capabilities — including home nursing visits, remote monitoring, telehealth check-ins, and digital data collection — represents both an opportunity and a design challenge where patient input is essential. Decentralization can dramatically reduce the participation burden for rare disease families, but only if the specific elements of decentralization are designed around patients' actual needs and technological capabilities.

Patient advisory input can determine which assessments can realistically be conducted at home, whether patients and caregivers are comfortable with wearable devices or video assessments, and how home-based and site-based visits should be balanced. For rare diseases where patients are geographically dispersed — often across national borders — these design decisions directly affect whether the trial can enroll a sufficient number of participants.

4x

Rare disease trials designed with patient-centered participation support *recruit four times faster* than those that do not.

ICON RARE DISEASE RESEARCH, 2024

SECTION 04

The Regulatory Mandate: Patient-Focused Drug Development

The argument for patient and caregiver engagement in clinical trial design is no longer simply a matter of best practice — it is increasingly a regulatory expectation.

The FDA's Patient-Focused Drug Development (PFDD) program represents a systematic approach for incorporating patient perspectives into drug development and regulatory decision-making. The agency has issued a series of methodological guidances that provide direction on collecting patient input, identifying outcomes of importance to patients, selecting or developing fit-for-purpose clinical outcome assessments, and incorporating patient experience data into regulatory submissions.

In December 2023, the FDA released its final guidance document on rare disease drug development, which explicitly emphasized patient and caregiver input as a key element of the development process. The guidance encourages sponsors to engage patients, caregivers, and advocacy groups throughout drug development — from early clinical planning through post-marketing surveillance. This is reinforced by the FDA's 2024 Rare Disease Innovation Hub, a cross-center initiative designed to coordinate rare disease activities across the agency, with patient engagement as a foundational element.

> REGULATORY CONTEXT
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> The Externally-Led Patient-Focused Drug Development meetings — public meetings organized by patient advocacy groups and attended by FDA — provide another channel through which patient perspectives formally enter the regulatory record. These meetings have been conducted for dozens of rare diseases and their outputs increasingly inform FDA reviewers' assessment of benefit-risk profiles.

For sponsors, the message from the regulatory environment is unambiguous: patient experience data, collected with sufficient rigor, can contribute to the body of evidence used in regulatory, payer, and prescriber decision-making. Trials designed without this data are leaving evidence on

the table — evidence that could make the difference between approval and a complete response letter, between broad access and narrow reimbursement.

SECTION 05

The Enrollment and Retention Dividend

Beyond the regulatory and scientific rationale, patient engagement in trial design delivers measurable operational benefits.

An analysis of rare disease trials found that those designed with a quality-by-design approach to participation support — which typically involves engaging with patient organizations and conducting qualitative research with patients to understand constraints and assess protocol feasibility — recruited four times faster than rare disease trials that did not employ this approach. This acceleration has profound financial implications given the high cost of each additional month of enrollment delay.

30%

clinical trial dropout rate

ACROSS ALL THERAPEUTIC AREAS

$19.3K

per lost patient

MINIMUM RE-ENROLLMENT COST

The retention impact is equally significant. The current clinical trial dropout rate across all therapeutic areas is approximately 30%, costing sponsors an average of at least $19,300 per lost patient in re-enrollment costs alone. In rare disease trials, where every participant is irreplaceable, the financial and scientific cost of dropout is even higher. Trials designed with patient-centered protocols — incorporating feasible visit schedules, relevant endpoints, reduced assessment burden, and strong support programs — consistently achieve better retention.

COMMON MISCONCEPTION

Sponsors can sometimes confuse patient urgency with unconditional willingness to participate. The assumption that because patients have serious unmet needs they will tolerate any level of trial burden is both inaccurate and counterproductive. Motivation does not override pragmatic financial, physical, and psychological considerations. Trial designs must respect the complex realities of patients' and caregivers' lives — and the only way to understand those realities is to ask.

SECTION 06

Practical Approaches to Meaningful Engagement

Meaningful patient and caregiver engagement requires more than a single advisory meeting or a cursory review of the protocol. The most effective approaches involve structured, ongoing partnerships that span the clinical development lifecycle.

Patient Advisory Workshops and Community Advisory Boards

Structured workshops that bring together patients, caregivers, advocacy leaders, and cross-functional sponsor team members have proven to be among the most productive engagement mechanisms. Effective workshops provide participants with an overview of the clinical development plan, present specific questions about protocol design, outcome measures, and participation burden, and capture structured feedback that is then incorporated into trial planning.

Community Advisory Boards (CABs) provide an ongoing governance mechanism, offering sponsors regular access to community perspectives as the trial evolves. CABs are particularly valuable for long-running programs where new questions arise throughout the development process.

Qualitative Research with Patients and Families

Qualitative research — including in-depth interviews, focus groups, and patient journey studies — should be conducted before protocol finalization to understand the symptoms of the condition, its natural history, its impact on patient function and quality of life, and the outcomes that are important and relevant to patients. This research should include patients and caregivers who will not be enrolling in the trial, to avoid biasing results.

> INNOVATIVE METHODOLOGY
>
> **Patient and Caregiver Perception of Change Assessments represent an innovative extension of qualitative research: video interviews conducted before, during, and after the clinical trial, with transcripts independently coded and themes analyzed by treatment group. This methodology captures patient experience data with sufficient rigor to contribute to regulatory submissions while providing context that standard outcome measures cannot.**

Advocacy Organization Partnerships

Patient advocacy organizations serve as both a conduit to the community and a repository of collective wisdom about the disease experience. Early, transparent engagement with these organizations — beginning at the stage of trial design rather than waiting until recruitment — allows sponsors to align their programs with community priorities and to build the trust that is essential for enrollment success.

This partnership must be genuine. Advocacy organizations are acutely sensitive to being used as marketing channels or patient recruitment tools. The most productive relationships are those in which the sponsor demonstrates authentic interest in the community's perspective, transparently communicates its goals and constraints, and follows through on the commitments made during engagement.

Patient-Reported and Caregiver-Reported Outcomes

The incorporation of patient-reported outcomes (PROs) and caregiver-reported outcomes (CROs) into rare disease trial protocols is both a scientific and ethical imperative. Many treatment outcomes in rare diseases are not adequately captured through laboratory tests, imaging, or clinician-assessed endpoints. Changes in fatigue, pain, emotional well-being, ability to perform

daily activities, and quality of life are often the outcomes that matter most to patients and families — and they are frequently the outcomes that differentiate a clinically meaningful therapy from one that is merely statistically significant.

The development and validation of PROs and CROs for rare diseases is challenging, given the heterogeneity of disease presentation and the absence of large normative datasets. However, the FDA's Patient-Focused Drug Development guidance provides a structured pathway for selecting, developing, or modifying fit-for-purpose clinical outcome assessments. Sponsors who invest in this process create a dual advantage: endpoints that are more likely to capture genuine treatment benefit, and a body of evidence that is more compelling to regulators, payers, and prescribers.

Caregivers can make or break participation in a clinical trial. We need to think about the whole family when designing trials that are both ***scientifically sound and ethically responsible.***

DR. HEATHER LAU, YALE UNIVERSITY

SECTION 07

Implications for Marketing and Medical Affairs

For professionals working in rare disease marketing and medical affairs, patient and caregiver engagement in clinical trial design is not a concern confined to the clinical development team. It has direct and significant implications for every downstream function.

Endpoint selection determines the value story

The endpoints chosen for a pivotal trial become the foundation of the product's value proposition. Endpoints developed with patient input are more likely to resonate with payers, prescribers, and patient communities because they reflect outcomes that these stakeholders recognize as meaningful. Conversely, endpoints that are clinically defensible but disconnected from patient experience create a persistent gap in the value narrative.

Trial design shapes market access

Inclusion and exclusion criteria from pivotal trials are routinely adopted as the basis for payer prior authorization requirements. Criteria that are too narrow limit the eligible patient population post-launch; criteria that do not reflect real-world clinical practice create barriers to access. Patient input at the trial design stage is an investment in post-launch market access.

Community trust starts in clinical development

The relationships a company builds with patients, caregivers, and advocacy organizations during clinical development are the same relationships it will rely on for disease education, patient identification, treatment adoption, and adherence support at launch. Companies that engage these communities authentically during trial design arrive at launch with a reservoir of trust and goodwill that money cannot buy after the fact.

Patient experience data strengthens every communication

The qualitative patient and caregiver data collected through structured engagement — video interviews, perception of change assessments, advisory workshop findings — enriches the evidence base available for medical affairs materials, advisory boards, health technology assessments, and payer dossiers. This data provides the human context that complements clinical statistics and makes the case for treatment value more persuasive.

Caregiver insight informs support program design

Understanding the caregiver experience during clinical trials provides direct insight into the support services that will be needed post-launch — from patient call centers to adherence programs to educational materials. Companies that listen to caregivers during development are better positioned to design support programs that work in the real world.

SECTION 08

Conclusion

The era in which rare disease clinical trials could be designed in isolation from the communities they serve is over. Regulatory agencies now expect patient and caregiver input. The evidence demonstrates that trials designed with this input perform better on every operational metric. And the patients and families who participate in these trials deserve to have their knowledge, their priorities, and their lived experience reflected in the studies that will determine whether a treatment reaches them.

For rare disease companies, the question is no longer whether to engage patients and caregivers in trial design, but how to do it well — early, authentically, and with the structural commitment to act on what is learned. The practical mechanisms exist: advisory workshops, community advisory boards, qualitative research, perception of change assessments, and advocacy partnerships. What is required is the organizational will to treat patient and caregiver engagement not as a compliance exercise but as a strategic asset.

The results speak for themselves: faster enrollment, better retention, more meaningful endpoints, stronger regulatory submissions, and — most importantly — therapies that are designed around the outcomes patients and families actually care about. In rare disease, where every patient

counts and every data point matters, there is no more powerful investment a sponsor can make than listening to the people its therapy is meant to serve.

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Rare Expertise

Rare Expertise is a strategic consultancy focused on helping companies developing and marketing products for patients with rare diseases. Our mission is to shorten the diagnostic and treatment journey in people with rare diseases through better education.

Rare Expertise and the Rare Medical Network work at the intersection of rare disease knowledge, clinical practice, and trusted professional networks. Our focus is on supporting healthcare professionals with credible information and access to expertise — when it matters most.

FOUNDED

Rare Expertise was founded in 2015 by Jack Davis and Jeff Sweeney, who are parents of children with rare diseases, and who both have extensive professional experience in marketing communications and medical education in rare disease markets.

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