Crossing the Finish Line

Why Effective Participation Support Strategy is Critical to Trial Efficiency and Success in Rare Diseases

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# Table of Contents

**Background** .......................................................................................................................................................... 3

**Executive Summary** ........................................................................................................................................ 4

**Critical Success Factors for Sponsors of Rare Disease Clinical Trials** .......................... 5

  - Recognize that motivation alone may not enable participants to “cross the finish line” ........ 5
  - Identify trial participation pressures as potential risks to trial conduct efficiency .................. 5
  - Engage with patient communities early to manage risks effectively ............................................ 5
  - Integrate participation support strategy into the trial risk management plan .............................. 5
  - Plan proactively  ................................................................................................................................. 5
  - Develop realistic trial implementation budget scenario ................................................................. 5
  - Inform sites and participants about participation support services ............................................. 5
  - Partner with experienced providers to identify and mitigate participation barriers .................. 5

**Methods** ............................................................................................................................................................... 6

**Key Findings** .......................................................................................................................................................... 7

  - Motivation is not enough ...................................................................................................................... 7
  - Trial participation exposes individuals to significant pressures ....................................................... 9
      - Financial pressures of trial participation ......................................................................................... 9
      - Physical and logistical pressures of trial participation ............................................................... 11
      - Psychological and emotional pressures of trial participation .................................................. 12
  - “Good” Participation Support According to Rare Disease Patients and Caregivers ........................ 13
      - Personalized and responsive support ........................................................................................... 13
      - Comprehensive and transparent support ...................................................................................... 14
      - Easy-to-access through a streamlined Point of Contact (POC) .................................................. 15

**Current Practice Deficiencies in Trial Participation Support** ..................................................... 16

**Reducing Participation Burden in the Clinical Development Ecosystem** ............................... 17

**Resources for Sponsors** ................................................................................................................................. 18

**APPENDIX I: List of Rare Diseases Represented in Survey Response** ..................................... 19

**About us** ............................................................................................................................................................ 20

**Contact Information** ....................................................................................................................................... 20
Background

Rare Disease clinical trials face unique challenges, such as low prevalence of disease and few qualified investigators, resulting in higher risks to clinical development programs for sponsors. For biotechnology companies, a Rare Disease clinical program may test their only asset or represent a significant part of their portfolio. Clinical trials are a source of hope for Rare Disease patient communities and may embody an individual's first or only opportunity to access a potential treatment. Efficiency in every aspect of trial design and conduct is imperative for both sponsors and patient communities, who share the common goal of delivering meaningful treatments to patients who urgently need them.

Providing certain types of trial participation support is of acknowledged importance; however, no systematic research has been conducted to understand the participation support needs of individuals affected by rare diseases or the effect of unmet participation support on trial participation and completion. A significant gap exists between the experiences and perceptions of individuals affected by rare diseases and the participation support services provided to them during clinical trials. Their perceptions of how effectively these services meet their needs are not typically assessed at the study level or at the macro level. While clinical research participation is a salient part of the patient journey of many rare diseases, no publications on this subject were found in the literature.

Scout Clinical (a patient logistic provider, or PLP) and PRA Health Sciences (a contract research organization, or CRO) partnered to carry out this first-of-its-kind research. The aim of this research was twofold: to amplify the voice of the Rare Disease community regarding clinical research and to provide sponsors with insight into effective participation support strategies to sustain the efficiency of clinical trials by addressing risks associated with participation burden.

Barriers to Understanding Participation Support Needs

The dynamic clinical research ecosystem contributes to this gap in understanding, including:

- It is not common practice for sponsors to collect data on participation support needs from trial participants before, during, or after a clinical trial— a very small number of sponsors have begun to do so.
- Surveys for collecting this data would require IRB/Ethics Committee approval and are ideally developed during early trial design. Participation burden and associated risks are not typically considered during this stage.
- During early trial design, sponsor teams are not typically aware of all participation support needs and participation support options relevant to the rare disease targeted, challenging their ability to proactively assess the potential effectiveness.
- Standard third party legal agreements only permit contact with trial participants related to trial operations and prohibit support service providers (such as PLPs and CROs) from conducting satisfaction surveys.

Overcoming Barriers to Gather Patient Insight

To overcome the above-mentioned systemic barriers and ensure strict compliance with contract agreements, Scout Clinical reached out to PRA’s Center for Rare Disease to leverage the Center’s close connections with rare disease patient communities and patient advocacy engagement expertise. The research was carried out by engaging a broad range of rare disease patient organizations to conduct virtual focus groups (vFG) and surveys with rare disease patients and caregivers.

Executive Summary

Our research was conducted between November 2020 and February 2021 and comprised a series of focus groups (n=4, total participants= 16) and a web-based survey with individuals affected by 69 unique rare diseases (n=126 responses).

Findings suggest that individuals have a variety of personal motivations for considering clinical research, and participants are highly motivated to complete the trials in which they enroll. We identified that trial participation exposes participants to significant pressures across three categories: financial, physical and logistical, and psychological and emotional. These pressures are incremental to the burdens participants already experience due to living with a rare disease. People affected by rare disease embarking on a clinical trial are running an endurance race they are highly motivated to complete; however, these incremental pressures negatively impact their ability or willingness to enroll or remain in clinical trials.

Research indicates that most sponsors don’t have a comprehensive and systematic approach to trial participation support. This was validated in our research which identified significant gaps in support in all three categories of participation pressures (i.e., financial, physical/logistical, and psychological/emotional). Participants in our research who had received trial participation support services reported instances in which these had effectively helped them overcome barriers to participation. This finding aligns with those of recent inquiries into equitable trial access in non-rare disease conditions and suggests that when implemented effectively, participation support services such as travel support and other forms of assistance reduce risks to the efficiency of trials such as poor enrollment, protocol amendments, and high drop-out rates\textsuperscript{2,3,4}.

Participants in our research reported that effective travel and participation support strategies must be personalized and responsive, comprehensive and transparent, and easy to access through a streamlined point of contact.

These insights point to several critical success factors for sponsors aiming to de-risk their Rare Disease clinical trials with an effective participation support strategy. They include cultivating a mindset shift that recognizes the active role that trial participants play in efficient trial conduct, engaging with patient communities to conduct participation burden assessments during early trial design, and implementing a participation support strategy in the clinical trial risk management process. Developing realistic budget scenarios for participation support with a risk mitigation frame of mind is key.

Results of our research raised two issues of relevance to equitable access to clinical trials and increased participation among underserved patient populations. First, whether regulators and ethical review boards must recognize that trial participation exposes individuals affected by rare diseases to incremental financial, physical, and psychological pressures that could be mitigated and which translate to reduced access or significant incremental burdens for some; and second, whether reducing participation burden would result in fewer negative participant experiences—helping change negative perceptions of clinical research among the general public.

\textsuperscript{2} Nipp R.D., et al. (2016) Financial Burden of Cancer Clinical Trial Participation and the Impact of a Cancer Care Equity Program. \textit{The Oncologist}, 21, pp. 467-474


Critical Success Factors for Sponsors of Rare Disease Clinical Trials

1. Recognize that motivation alone may not enable participants to “cross the finish line.”

Cultivating a mindset shift to recognize that participants’ motivation to join or remain in a trial is balanced with practical realities of living a complex daily life already impacted by the burden of disease. Those constraints can and do limit willingness and ability to participate.

2. Identify trial participation pressures as potential risks to trial conduct efficiency.

Patients and caregivers must be willing and able to complete a broad range of tasks for a trial to run efficiently. These tasks add pressures that are incremental to the burden of rare disease. As a result, participants may struggle or be unable to “cross the finish line,” translating to increased risks of poor enrollment, drop-outs, and screen failures.

3. Engage with patient communities early to manage risks effectively.

People affected by rare diseases are best placed to offer insight into the incremental burdens and, therefore, the potential risks of taking part in a trial. Engaging with patient communities at the earliest stages allows sponsors to explore options without the constraints imposed by an approved protocol.

4. Integrate participation support strategy into the trial risk management plan.

Sponsors and all stakeholders in the clinical research ecosystem should develop risk mitigation strategies to manage risks driven by participation burden on the efficiency of a planned trial.

5. Plan proactively.

Participation burden risk management should be an integral part of trial design and conduct and begin in the earliest stages of protocol design. Mapping trial participation support requirements by engaging with patient communities will engender commitment from leadership and provide lead time for support services implementation. Best practices include gathering patient feedback on draft protocol synopses and on anticipated “real life” participation burden and participation support needs.

6. Develop realistic trial implementation budget scenarios.

Developing budget scenarios with realistic cost estimates for participation support services (i.e., those relevant to mitigating participation burden risks) requires consultation with third-party providers. Starting these consultations early can ensure budgets are realistic and identify important country-specific regulatory and cultural considerations. Coordinating early with third-party providers such as Scout Clinical and PRA can ensure participation support budget scenarios are realistic and address key trial risks.

7. Inform sites and participants about participation support services.

Site teams and participants should be proactively informed about the participation support options available for a trial. Our research suggests that availability of support services impacts participants’ decisions to join or stay in a trial and that, at times it influences PI decision-making as to which trials they recommend to patients. One strategy sponsors sometimes employ is to instruct site teams that participation support services should only be provided by request. Our research suggests this is an ineffective approach, as many participants will not be aware and will not ask for accommodation – opting instead to drop out or forego trial participation.

8. Partner with experienced providers to identify and mitigate participation barriers.

To overcome barriers and develop and implement effective participation support measures, sponsors should partner with a range of third-party providers. Key activities include engaging with patient communities to identify participation burdens, scope participation support services, and develop a strategy aligned to regulatory considerations of different trial geographies. Teaming with experienced providers such as Scout Clinical and PRA is vital to implementing participation support that reduces trial risk.
Methods

A list of rare diseases with either a) active clinical development or b) management services provided by Scout Clinical and/or PRA between 2015-2020 was developed. No further criteria were applied to the selection of diseases for this research.

Recruitment for participation in this research was conducted by the Patient Advocacy Strategy (PAS) team within PRA’s Center for Rare Diseases. Recruitment for Virtual Focus Groups (vFG) was performed by outreach to patient organizations associated with the list of rare diseases identified as having had active clinical development. Recruitment for participation in the survey was carried out through email and social media outreach to rare disease patient organizations in North America.

To avoid bias, it was not known whether vFG participants and survey respondents had enrolled in Scout- or PRA-affiliated studies. No data or information that could be used to determine this was solicited. It is therefore not known which specific studies comments made by participants in this research relate to, and it is not known whether Scout or PRA (or both) were involved in the conduct of those studies.

- vFG (n=4, total participants= 16), convenience sample of individuals affected by RD, patients and caregivers, who had taken part in at least one clinical trial:
  - All participants were North American (US or Canada).
  - Each vFG was 90 minutes in duration.
  - Recruitment took place via PRA’s PAS team outreach to Rare Disease patient organizations associated with rare diseases with active clinical development between 2015-2020.
  - vFGs were carried out by PRA’s PAS team.
  - Participants each received a $125 honorarium as compensation for their time.
  - vFGs took place during December 2020 and February 2021.

- Online survey (133 responses, of which 126 responses were valid), open to all individuals affected by rare diseases as a patient or caregiver, regardless of whether or not they have taken part in a trial:
  - Recruitment took place via PRA’s PAS team’s partnership outreach to Rare Disease Organizations in North America.
  - Respondents included individuals affected by 69 rare diseases.
  - The majority of respondents were North American.

- Respondents were recruited by PRA’s Patient Advocacy Strategy team through email and social media outreach to North American Rare Disease patient communities.
- Respondents were entered into a draw for one of four prizes, one grand prize comprising a $100 gift card and a $500 donation to the Patient Organization selected by the winner, and three prizes of $100 gift cards each.
- The SurveyPlanet™ platform was used to implement the survey.
- The survey was open between 26 January 2021 and 19 February 2021.

Focus group data were transcribed and analyzed, and insights gained were used to develop a subsequent survey.
Key Findings

Motivation is not enough.

Deep personal motivations inform joining a clinical trial; participants are running an endurance race they are highly motivated to complete, but motivation is not enough.

Our research clearly indicated that motivation for trial participation is high. Focus group participants reported a variety of deep, personal motivations for taking part in clinical research. Nuances in drivers of participation were evident and included: excitement for groundbreaking clinical research; a desire to contribute to the scientific understanding of the condition; monitoring the patient’s health, inspiration, and motivation imparted by patient advocates; patient’s burden of disease and burden of existing treatment; and lack of other treatment options. All participants were readily able to identify their exact motivation(s) for attempting to take part in clinical trials, and their ambition for successful completion of the trials they engaged in was evident.

Hurdles during the trial participation journey

However compelling their motivation to participate in and complete trials, respondents reported pressures imposed by trial participation negatively affected their ability and/or willingness to do so. Managing these pressures in addition to pressures they already experienced due to the burden of disease at times exceeded individuals’ material, physical or psychological resources.

Efforts to reach the finish line

Despite the incremental nature of these pressures, nearly all focus group participants described determined efforts to overcome them in order to complete the trials they started. For some respondents, these efforts were not enough. This pragmatic reality contrasts with a general perception within the drug development ecosystem that, due to the high unmet need within rare disease, motivation suffices to ensure a participant’s ability to clear some, or all, of the hurdles of trial participation.

Focus Group Insights

“The reason I wanted to participate is that I’ve been diagnosed for 40 years right now, and back then what you were told was that this condition is so rare that no one’s ever going to do studies on it … So just the fact that, oh my gosh, there is a clinical trial going on right now, isn’t that great?!”

“Well, the first study we were in was a year after my son was diagnosed and he was patient #1 for that study… We were just trying to look for something to find a baseline and keep him steady on that baseline.”

“We actually have four kids that have the same type of thalassemia as our son. But he was the one child who specifically had said repeatedly that he didn’t want to have thalassemia anymore. He didn’t want to have to get transfusions. He didn’t want to miss school. So, we kind of sought out the trials.”

Impact of participation support services

Participation support services reported by virtual focus group (vFG) participants varied in terms of type of service and range of services made available to them. The least comprehensive participation support reported by a participant was restricted to reimbursement for parking during trial visits. The most comprehensive included assistance with organizing all travel logistics, per-diem payments, and provision of overnight accommodation. All vFG participants reported experiencing at least some gaps in support that impacted their willingness or ability to take part in a trial. Only some participants reported requesting the additional support they needed. Of those who requested changes to their participation support services, most reported being able to obtain these to some extent and that it enabled them to continue in their trial.

Thirty-seven percent (37%) of survey respondents (n=46) reported they had taken part in at least one clinical trial; however, only 67% reported that they had received any participation support services, such as travel support or financial assistance.
Of those who did receive participation support services, 71% reported that having these services somewhat or definitely impacted their ability to participate in and complete the trial(s). Satisfaction with services provided was significant. Approximately half of survey respondents indicated they were very satisfied with the services they received.

Overall, 84% of survey respondents (n=126), including those who had and had not participated in a trial, stated that receiving participation support services would somewhat or definitely impact their ability or willingness to take part in a future trial (see Figure 10).

A key implication is that participation support services are highly relevant to reducing risks to the efficiency of rare disease clinical trials such as poor enrollment, high dropouts, and resulting timeline delays.

Focus Group Insights

“We would have made it work to be able to participate if there was any way that we could have. But to have to commit to being away from home for 6 months and have to relocate for that long, just all the daily costs of everything even housing for so long, I mean, we would have tried to do it (if support was not available), but we would have been in major debt to do it.”

“My daughter has a history of status seizures, which are really hard to control and stop so she has to be near a hospital for emergency at all times. So the safest thing was to actually map it out and find out all the hospitals and emergency locations along the way (to the trial site). The coordinator mapped our driving route for visits so that we could get the fastest emergency services response if something happened.”

“We were recently offered to participate in another (trial), but because of those reasons, (having) no place to stay and having to be exposed to so many people (during COVID) throughout the trial, and you know, the job security and the income… we had to decline the offer of participating, which was really hard for us because she does need it and we do need something different and new, because everything that’s offered right now doesn’t work.”
Trial participation exposes individuals to significant pressures

Trial participation exposes individuals to pressures that become hurdles on the way to the “finish line.”

Virtual focus group (vFG) participants shared experiences that revealed a broad range of pressures. These were driven by myriad factors, some of which were highly contextual (related to the specific disease or personal circumstances) while others were almost universal—navigating complex and unfamiliar environments such as airports, unfamiliar hospitals, and hotel lodgings.

These could be categorized into three main types of participation pressures:

- Financial
- Physical and logistical
- Psychological and emotional

Financial pressures of trial participation

vFG participants identified financial pressures arising from expenses incurred due to a range of circumstances, including trial policy explicitly not covering certain participant expenses, barriers to being reimbursed for certain items covered by the trial, and lost income due to time required for trial visits.

Trial policy exclusions included high dollar value expenses such as airfare for site visits, wheelchair accessible rental vehicles, or overnight accommodation. They also included ‘hidden costs’ such as childcare costs or mileage.

Managing receipts and awaiting reimbursement were identified by some focus group participants as a source of financial pressure. Receipts are not available for all expenses (e.g., gratuities for luggage handling). Paying out-of-pocket and awaiting reimbursement had a significant impact on their financial circumstances.

Finally, some vFG participants reported that lost income due to trial participation was a significant financial pressure. One individual reported constant worry about their partner losing employment if they were unable to return to work in time after traveling to a site visit. That economic instability was one key reason they were declining participation in other trials offered to them.

Fifty percent (50%) of survey respondents indicated that they sometimes or frequently experience financial difficulties.
Living with a rare disease can significantly impact the financial health of individuals and families affected due to increased costs associated with managing the condition, including direct medical costs, and indirect costs such as professional caretaker/assisted living services, loss of work income, and reduced employment\textsuperscript{5,6}. The results of our research suggest that current participation support practices leave trial participants with incremental financial pressures, which become barriers to joining or completing a trial. This emphasizes the importance of considering the financial pressures that may be associated with participation as a key to rare disease trial risk assessment.

Focus Group Insights

“It would’ve been great to have reimbursement for some of our child care costs during that time because we’re fortunate that we could make it work, you know…we had the money in the bank to be able to do that, but a lot of families do not have that option. They’re going to be completely stressing out about that side. So, I think that child care can be a determining factor for some families and whether or not, they can do these trials…I know friends who want to do the trial and they’re like, there’s no way.”

“I got to the hotel (for an overnight study visit) and they didn’t have my reservation, they were going to make me pay for it. Which sadly at that time I didn’t have ‘open to charge’ which was embarrassing. I do now but back then I was a bit strapped for cash and it was embarrassing.”

“…with my husband’s job, we live in a state where they can fire at will for any reason. So even with medical reasons on board, he could have potentially been fired (for absences due to trial visits). And he was fired at one point for this reason. So we just wanted to make sure that we were able to keep a steady income, a job… We were constantly worried about if we couldn’t get back (in time) if my husband would have a job.”

“They’d say “well save your receipt from the gas station” (for reimbursement) which sounds fine, but inevitably I would be getting gas and the gas thing would be out of paper and it would say ‘come inside’. And I’m like ‘I can’t come inside, I’ve got my child in the car…’ so I couldn’t do it and so then I’m out 50-60 bucks right there.”

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6}
\caption{How would you describe your household’s financial circumstances?}
\end{figure}


Physical and logistical pressures of trial participation

Physical and logistical pressures reported by vFG participants arose when navigating complex environments such as airports or lengthy drives, navigating unfamiliar health care environments, and receiving care from professionals who were unfamiliar with their needs.

Physical pressures included strain, discomfort, anxiety, fatigue, and pain. These were primarily reported by parents who were traveling to site visits on their own with a child participant. This arose from having to single-handedly manage logistical pressures such as navigating an airport or transit with a child patient, as well as carrying luggage and equipment through complex environments like airports or car rentals. In one extreme case, a participant reported that she experienced a life-threatening thrombotic event due to plane travel while accompanying her child to a site visit.

Physical pressures were also reported by participants who had to travel home from site visits while feeling very unwell after a site visit; these were due to assessments and procedures, having to maintain awkward postures for a long period of time (e.g., holding a child), or standing for hours to await testing at a trial visit. Some reported this as a barrier to taking part in or completing clinical trials.

No vFG participants reported receiving any support for managing the physical pressures associated with participation — this finding is not surprising, as this is not typically offered to trial participants. However, some reported requesting accommodations, such as reimbursement for driving instead of flying, to avoid navigating airports or the reverse.

Although our survey sample was modest, 75% of respondents reported living in rural or suburban settings. As these settings are typically at a distance from academic and specialist centers, travel and associated physical and logistical pressures are likely to be relevant considerations for our survey cohort.

As Rare Disease clinical trials typically take place at relatively few sites, the physical and logistical pressures associated with trial participation are likely to remain significant for participants.

Participation support to address or remove the “hurdles” that participants encounter will remain important.

Focus Group Insights

“I would have to go pick up the (stipend) check at the opposite end of the hospital after fasting all day. And (after) all of my labs. Literally the physical expense of getting the check was often not worth it because I would leave these appointments very, very sick. Very sick. And then have to get myself to the airport and fly 10 hours home and then get myself home at like midnight. Just to be home so I could not miss another day with my kids and go to work.”

“We were waiting in the blood lab for a very long time…there’s been days we’d really, really stay in there for 5 hours and it’d be so full we couldn’t even sit down. And my daughter doesn’t have a chair so we have to hold her the entire time. And she’s 8, so she’s quite heavy.”

“The trip was exhausting. My husband came with me the first time, so he was the driver (that time) and I felt exhausted and I couldn’t ask him to do that every 2 weeks, I might (have been) able to deal with it every 8 week.”

“I had like, 30 minutes to get to the other side of the airport. I’m like running, with my kid. It was, it was horrendous. That was 8 years ago… No one had told me that you shouldn’t cross your legs on a flight for a long time because you can get blood clot, and I ended up crossing my legs because she was screaming the entire flight, which was awful. And so the next day I ended up having a TIA stroke because of the blood clot. So, it was really stressful.”

![Figure 7](image)
Psychological and emotional pressures of trial participation

Psychological and emotional pressures of trial participation were reported by the majority of vFG participants. Some psychological pressures were mentioned directly by participants, while others could be inferred from actions participants reported taking to mitigate them.

Participants reported a broad range of drivers of these pressures. These included the impact of participation on other family members; social isolation or loss of support structures, such as being away from their partner or losing access to counseling support during lengthy out-of-state trial visits; being hyperaware of their condition or feeling that their “condition is on display.” Financial and physical pressures were also mentioned as drivers of psychological and emotional pressures, for example, fear of loss of employment due to time requirements or physical exhaustion during site visits or travel to sites.

Some parents reported experiencing anxiety or worry about whether trial participation for an experimental drug is right for their child, as well as pressures arising from witnessing their child experience pain or difficult procedures throughout their trial participation.

Only one vFG participant reported receiving psychological support—this is unsurprising, as psychological support is not typically offered to trial participants.

Interestingly, approximately 30% of survey respondents identified emotional support/counseling as being a service that could make it easier for them to participate in a clinical trial.

Living with a rare disease that affects an individual or their loved one has a profound impact on psychological and social wellbeing.7,8 Our research suggests that taking part in clinical trials can add significant incremental psychological and emotional pressures for participants. Support for trial participants to help them cope with these incremental psychological and emotional pressures related to their participation is not typically offered.

Focus Group Insights

“I had a period of time where I was having panic attacks during this time in the trial and felt (a) very (significant) lack of support. I ended up needing medication, and even when it came to that, it was something out of pocket that I had to pay out of pocket, for counseling services.”

“I have people that are like, ‘oh, my gosh, I can’t believe you let your kid be a guinea pig,’ and so you have that guilt and you’re a parent, and you’re like, I’m doing the best I can, and I want the best for my kid, but am I doing the right thing? And so you have a lot of doubt and guilt and anxiety that I think we put on ourselves.”

“It starts to accumulate as you’re in the trip, especially if you’re doing a week-long trial… I remember one particular experience, it was like day 5, we were running all over the hospital, and he had cognitive evaluation and I mean it was just a mess (of a) day… and he just lay down on the ground of the hospital… and I was like ‘I’m done’… and this man that worked in the hospital was like “Ma’am, don’t let your child lay down in the middle of the ground” … and I was like ugh! (exasperation emphasis) that’s the least of my concern right now… it’s such an emotional experience, you really can’t over look that emotional bit of help that just having somebody else there beside you can do.”

Taking part in clinical research is seen as having psychological benefits associated with hope by many individuals affected by rare diseases. Our research, although modest in sample, suggests that psychological benefits are also accompanied by significant psychological and emotional costs for many participants.

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“Good” Participation Support According to Rare Disease Patients and Caregivers

Virtual focus group (vFG) participants were asked what their ideal participation support offering looks like. Discussions around what worked and didn’t work for participants in prior trials helped to identify key features and services.

“Good” participation support is:

• Personalized and responsive
• Comprehensive and transparent
• Easy to access through a streamlined point of contact

Personalized and responsive support

Personalized and flexible support services enabled participants to overcome predictable and unpredictable barriers to participation. Respondents identified a multitude of highly individual and contextual barriers encountered during trial participation. Flexibility to adapt support levels to the participant as their circumstances evolved throughout trial participation was effective in helping them to continue with the trial. The reverse was true where flexibility was not available.

Focus Group Insights

“I mean, when COVID came around, there was no hesitation. It wasn’t, do you want to Uber or would you rather have a rental car? It was, okay, so I have a reservation for a rental car for you while you’re here so that you won’t have to have exposure. So, our sponsor has been very generous in making sure that all those kinds of things were taken care of”.

“I’m not excited about staying in the hotel ... I don’t know if that’s safe when you’re in a pandemic. So I asked if we can go to an AirBnB instead within a price range and they said yes. So we’re going to be doing that this time. They’re pretty flexible on things. If you ask. So we’ve been fairly satisfied with that.”

“They’ve just been really accommodating with if one (trial) site had a high rate of Covid or that state did, making sure they could go to another state for their visit.”

“The coordinator mapped our driving route for visits so that we could to get the fastest emergency services response if something happened. She would let us know by email along the way if there was a route that had, like a delay or an accident, or some reason we couldn’t get through, so that we didn’t end up stuck somewhere with her if she was to have an emergency situation type of event. Which I thought was extremely helpful.”
Comprehensive and transparent support

vFG participants identified participation barriers related to all three categories of trial participation pressures (i.e., financial, physical and logistical, and psychological and emotional). ‘Comprehensive’ support across all three categories was reported as being valuable and having an important impact on the trial participation experience.

When asked to envision an “ideal” trial participation assistance package for themselves, participants expressed a desire for “holistic” support and “navigation” style assistance they could rely on through all the challenging aspects of clinical trial participation.

Focus Group Insights

“But the 2nd trial I was spoiled rotten to the core! (laughter) That travel agency located in Massachusetts that the hospital dealt with was fantastic! They would send me an itinerary of all my travel via email, they of course booked my airfare to and from Detroit and they arranged for a limousine ride… a beautiful limousine ride from the airport to my hotel and again the travel agency had made the hotel arrangements ahead of time for me.”

“(The doctor) said in that meeting that we were good candidates for 2 different medical trials. And then he said, oh, by the way, because it’s like a 4 hour drive and- we were just going to come back and we were exhausted- he said, ‘well, this trial pays money’. And I had never heard of that before and I know it sounds really stupid. I’d never heard about reimbursement or per diem or anything. I was like, okay. And so it was me and my nurse, and then my daughter and so… the study pays for us to go up there, for my nurse to have her own hotel room, and then they pay for all of our food. And they pay mileage, I think. And so that was the only way that we were able to do it for as long as we were.”
Easy-to-access through a streamlined Point of Contact (POC)

The majority of vFG participants expressed a desire for a single POC who they could turn to for assistance throughout a clinical trial. One participant stated that ideal participation support would resemble the “Make a Wish Trip” model, where all logistics arrangements are made by a navigator who accompanies them throughout the entire trip, serving as a single POC for their needs. Another participant expressed the desire to be accompanied throughout the trial journey by someone who could be a resource for information, assistance, and support.

Nearly 62% of survey respondents indicated that receiving trial navigation support from someone to help organize and manage their activities during the trial would make participation easier. This suggests a compelling need for personalized assistance through a single POC during trial participation across a broad range of Rare Diseases.

Focus Group Insights

“We did that Make a Wish trip and if you could model something off what is “the ideal” (service) it’s the Make a Wish Trip model. Where they meet you at the airport, as soon as you get off the plane they’re there. They help you down to the baggage, they stay with you while your bag is being picked up. They walk you out to the rental car, put you into the rental car. People think ‘oh that’s not that much’ but it’s tremendous. They think about everything with Make a Wish so that you’re not having any moment of stress. And so that’s kind of what I would like. Meet me as soon as I get off that plane, because I’m going to be frazzled for one thing, trying to keep him (my son) occupied on the plane, and then I have to go collect all the stuff and try to get to the rental car to get to the hotel.”

“Somebody that could be by their side through the entire process, not a phone number where they might get a different person each time. But, like, [they would be] participating in the trial with them, as their partner, as the person that they know is gonna be, maybe at the airport to pick them up. They’re going to go to the hotel with them. They’re going to make sure they get checked in. They’re going to make sure they know where the grocery store is that they need to go to; if they have religious services they want to attend in the area; if there’s a language service that’s needed. This is somebody that they have their number. They can text them. They know that they’re gonna respond. They know they’re going to be able to have an answer and if they don’t have an answer, they kind of know where to get the answer.”

Figure 11

<table>
<thead>
<tr>
<th>IS THERE ANYTHING ELSE THAT COULD BE PROVIDED TO MAKE IT EASIER FOR YOU TO PARTICIPATE IN A CLINICAL TRIAL (FREE OF CHARGE?)</th>
<th>TOTAL RESPONSES = 126</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigation support - someone to help you organize and manage what you need to do throughout the trial</td>
<td>78</td>
</tr>
<tr>
<td>List of travel/participation services available to select from</td>
<td>74</td>
</tr>
<tr>
<td>Education/training about practical aspects of taking part in clinical trials</td>
<td>67</td>
</tr>
<tr>
<td>Household support like pet care, care for other dependents, house sitting</td>
<td>44</td>
</tr>
<tr>
<td>Emotional support/counseling</td>
<td>37</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
</tr>
</tbody>
</table>
Current Practice Deficiencies in Trial Participation Support

No standard participation support/assistance is prescribed by clinical trial regulations, so there is significant variation in the services provided to mitigate the different pressures of clinical trial participation for individuals.

Sponsor preference, site acceptance/uptake, and variances in what are considered acceptable forms of support between different regulators contribute to this variation. However, recent literature has highlighted that these systemic barriers limit access to clinical trial participation and contribute to impeding equity and diversity in clinical research.9,10,11

Half of the respondents to our survey reported they sometimes or frequently experience financial difficulties, and, for many rare diseases, clinical research is a key aspect of the patient treatment journey. This correlation would indicate that equity and access impact a significant number of patients and caregivers affected by rare diseases.

More than 70% of survey respondents reported that if they were not able to receive the participation support services they need, their ability to take part in a trial would definitely or somewhat be impacted.

Focus Group Insights

“I don’t think I’d feel well enough to do both trips in one day. I just, pulled out (of the trial) for that reason after the 1st treatment. If it was possible to have a car take me to the clinical trial… I think I would have stuck with it despite the other problems I had there. To me that was a huge cost whereas their expenditure if they helped me out getting there would have been negligible …thinking through a lot of the barriers that make people decide that they won’t participate in a trial, like number one would be child care and so anything that can help remove that as a decision-making factor that would make somebody say ‘no, we can’t do that’ would take away barriers.”

“If it had been a year or two later, I would not have been able to participate in that trial because I was just in a different economic circumstance and work circumstance by that point. So it was just a very unique period of time in my life that made it possible. And really I think very few people can put forth that kind of effort with no additional help.”

Figure 12

IF YOU WERE NOT OFFERED THE SERVICES YOU SELECTED, WOULD IT POTENTIALLY PREVENT YOU FROM BEING ABLE OR WILLING TO TAKE PART IN A CLINICAL TRIAL?

TOTAL RESPONSES = 126

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>I’m not sure</td>
<td>13%</td>
</tr>
<tr>
<td>No, not at all</td>
<td>17%</td>
</tr>
<tr>
<td>Yes, definitely</td>
<td>20%</td>
</tr>
<tr>
<td>Yes, somewhat</td>
<td>51%</td>
</tr>
</tbody>
</table>


Reducing Participation Burden in the Clinical Development Ecosystem

Results of our research raised two broad issues of relevance to make clinical trials more accessible and less burdensome to individuals living with the already high burden of a rare disease: the role of regulatory perspective on participation support practices; and the implication of positive and negative trial participation experiences.

Trial participation appears to add incremental burden to individuals already living with the burden of a rare disease. We argue for a need for regulators and ethics boards to shift perspective from regarding certain forms of participation support as potentially coercive to considering comprehensive participation support, as necessary, to:

a. ensure equitable access to trials – an especially salient consideration in current efforts to ensure diversity in clinical trials, as practical barriers to trial participation are recognized to disproportionately affect underserved populations; and

b. protect individuals who already experience a high burden of rare disease from the added incremental burden of trial participation that could be mitigated – the principle that every effort must be made to remove or mitigate negative impacts experienced by subjects taking part in research of all forms is already well established.

Our research also suggested that individuals' experiences of clinical trial participation, positive and negative, influence their perceptions of clinical trials, sponsors, and health care providers. Individuals share their positive and negative experiences with others in their rare disease communities. Reducing participation burdens experienced in clinical trials could result in more positive participant experiences and raise the profile of participation among groups that may have reservations about taking part in trials.

There is a staggering unmet need for new and meaningful treatments for rare diseases. When clinical research is as efficient as possible, patients, sponsors, and all other clinical development stakeholders win.
Resources for Sponsors

From PRA Health Sciences

The Patient-Centric Trial Development Toolkit – Rare Diseases
Developed by a team of experts from our Center for Rare Diseases and available at no cost to clinical development sponsors, this toolkit includes four digital resources designed to mitigate risks that frequently occur in rare disease clinical trials and to support new patient-centric practices that promote trial participation. Click for free download.

Patient-Centric Protocol Risk Assessment Tool – Rare Diseases
This self-assessment tool guides sponsors or patient organizations through a structured approach for rapid risk-assessment of participation burden for a specific clinical trial design. Risk mitigation strategies are provided for consideration. Developed and validated by experts and easy to use whether patient-centricity is new or well established within your team. Click for free download.

Rapid Participation Burden Assessment Tool – Rare Diseases
This tool was developed to help you, the sponsor, gather study-specific feedback directly from patient communities on aspects of your rare disease trial that may be challenging for participants. This may help guide trial design to mitigate risks of recruitment failures, retention failures, protocol amendments and other inefficiencies and improve participation experience. Click for free download.

Patient Involvement Value Dossier
This dossier outlines emerging evidence of benefits/ROI of patient involvement in the trial development process from recent literature and provides illustrative case studies from PRA’s Center for Rare Diseases. Click for free download.

Patient Engagement Support
PRA’s Center for Rare Diseases provides patient engagement support including patient organization outreach, patient and caregiver protocol reviews and participation burden assessments for pre-clinical and clinical stage sponsors.

From Scout Clinical

Services by Scout Clinical
Scout Clinical’s full range of patient services benefit the Sponsor, CRO, Site Personnel, and most importantly, the patient. https://www.scoutclinical.com/services

Scout Portal
The Scout Portal was hand-crafted by Scout Clinical. It provides the flexibility to accommodate the unique needs of every sponsor, study, country, site and patient including reporting, transparent billing and regulatory compliance. It can be accessible to patients, caregivers and sites and it is translated in over 200 languages. https://www.scoutclinical.com/services/scout-portal

Regulatory
Scout Clinical is fully compliant with all data privacy and regulatory requirements in the countries where we operate. We prepare Informed Consent Form language and other patient-facing documentation that is compliant with all local and central Independent Review Board and Ethics Committee requirements. Our goal is to make compliance with the wide array of data privacy obligations as simple as possible. https://www.scoutclinical.com/services/regulatory

Patient Liaison
Scout Clinical takes an innovative approach to patient services, customizing our services to meet the needs of each patient on a visit-by-visit basis. Our in-house team of Scout Patient Liaisons serve as the dedicated point of contact for patients and caregivers throughout the lifecycle of each study. https://www.scoutclinical.com/about/patient-liaison
APPENDIX I: List of Rare Diseases Represented in Survey Response

Responses included individuals affected by:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Sphingomyelinase Deficiency (ASMD)</td>
<td>IBMPFD (aka VCP Disease)</td>
<td>Pityriasis Rubra Pilaris (PRP)</td>
</tr>
<tr>
<td>Aicardi Syndrome</td>
<td>Idiopathic Hypersomnia</td>
<td>Pompe Disease</td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>Idiopathic Optic Atrophy</td>
<td>Postural Orthostatic Tachycardia Syndrome (POTS)</td>
</tr>
<tr>
<td>Arachnoiditis</td>
<td>Idiopathic Pulmonary Fibrosis</td>
<td>Pityriasis Rubra Pilaris (PRP)</td>
</tr>
<tr>
<td>Bacterial Myositis</td>
<td>IgG Subclass Immunodeficiency</td>
<td>Pompe Disease</td>
</tr>
<tr>
<td>Behcet’s Disease</td>
<td>Klippel Trenaunay Syndrome</td>
<td>Primary Biliary Cholangiitis (PBC)</td>
</tr>
<tr>
<td>Bronchiolitis Obliterans Syndrome (BOS)</td>
<td>Leiomyosarcoma</td>
<td>Primary Immune Deficiency (PID)</td>
</tr>
<tr>
<td>CDKL5 Deficiency Disorder</td>
<td>Lennox Gastaut Syndrome</td>
<td>Retinitis Pigmentosa</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Loss of 16p12.2.</td>
<td>Sanfilippo syndrome type A (MPS IIIA)</td>
</tr>
<tr>
<td>Chronic Regional Pain Syndrome</td>
<td>Malan Syndrome</td>
<td>SATB2-associated syndrome</td>
</tr>
<tr>
<td>Classical Homocystinuria</td>
<td>Marshall Smith Syndrome</td>
<td>Sickle Cell disease</td>
</tr>
<tr>
<td>Common variable immune deficiency (CVID)</td>
<td>Mast Cell Activation Syndrome (MCAS)</td>
<td>Smith-Magenis Syndrome</td>
</tr>
<tr>
<td>Complex Regional Pain Syndrome</td>
<td>Metachromatic Leukodystrophy</td>
<td>Snyder-Robinson Syndrome</td>
</tr>
<tr>
<td>Costello Syndrome</td>
<td>Microvillus Inclusion Disease</td>
<td>Usher Syndrome type 1F</td>
</tr>
<tr>
<td>Cystinuria</td>
<td>Morquio A Disease (MPS4A)</td>
<td>Xeroderma Pigmentosum</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy (DMD)</td>
<td>Myasthenia Gravis</td>
<td></td>
</tr>
<tr>
<td>Ehlers Danlos syndrome</td>
<td>Myelodysplastic syndrome</td>
<td></td>
</tr>
<tr>
<td>Fabry Disease</td>
<td>Myelodysplastic syndromes (MDS)</td>
<td></td>
</tr>
<tr>
<td>Fibrodisplasia Ossificans Progressiva (FOP)</td>
<td>Narcolepsy</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Stromal Tumor (GIST)</td>
<td>Niemann Pick Type C</td>
<td></td>
</tr>
<tr>
<td>Gaucher Disease</td>
<td>Noonan Syndrome</td>
<td></td>
</tr>
<tr>
<td>Glutaric Aciduria Acidemia Type 1</td>
<td>Okur-Chung neurodevelopmental syndrome</td>
<td></td>
</tr>
<tr>
<td>GM1 Gangliosidosis</td>
<td>Pallister-Killian Syndrome</td>
<td></td>
</tr>
<tr>
<td>Hemophagocytic Lymphohistiocytosis</td>
<td>Paroxysmal Nocturnal Hemoglobinuria (PNH)</td>
<td></td>
</tr>
<tr>
<td>Hereditary Hermorrhagic Telangiectasia (HHT)</td>
<td>Pfeiffer Syndrome</td>
<td></td>
</tr>
<tr>
<td>Hypokalemic Periodic Paralysis</td>
<td>Phelan-Mcdermid Syndrome</td>
<td></td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Phenylketonuria</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>PIK3CA mutation</td>
<td></td>
</tr>
</tbody>
</table>
About PRA's Center for Rare Diseases

At The Center for Rare Diseases, we never forget that rare diseases alter entire lives. We’re committed to changing that. Our experience allows us to efficiently conduct rare disease studies by anticipating and mitigating risks while maintaining focus on the patient, the family, and their quality of life. We understand that every day without treatment means another day filled with doctor’s appointments, lab work, postponed opportunities, and canceled plans.

The time and effort spent by the patient and their loved ones in managing a rare disease is time better spent on living a fuller life. We dedicate our time to rare disease research so they don’t have to.

About Scout Clinical

Scout Clinical offers comprehensive patient services that are adaptable to fit the precise needs of clinical trial participants on a global scale. We offer a stress-free, confidential, and personalized approach to promote effective participation by reducing patient and family burden through fully coordinated pre-paid services and expeditious reimbursement. To find out more, visit us at https://www.scoutclinical.com/.