Pharma Intelligence
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Rare Disease Trial Strategies

WHITEPAPER

Daniel Chancellor
Thought Leadership Director, Informa Pharma Intelligence

Citeline
Informa Pharma Intelligence

Introduction

For many patients with rare diseases, finally receiving a diagnosis is a major milestone, but a lack of proven treatment options means that their prognosis is unchanged. Approved drugs are available for just 5% of the approximately 7,000 rare diseases identified so far[1], many of which are life-threatening or life-limiting. The pharmaceutical industry is making inroads through R&D despite the unique challenges facing clinical trials for rare diseases, not to mention often navigating without regulatory precedents and with an uncertain commercial outlook. Progress can therefore feel slow in spite of the priority that many drug companies place on these patients and their unmet needs.

Our white paper focuses on clinical trials, aligning the latest trends in rare disease R&D viewed through the lens of Citeline's gold-standard clinical intelligence with unique patient insights uncovered in a survey conducted in partnership with Rare Patient Voice. From this, we can share a set of practical recommendations for study sponsors to adopt in their approach to clinical trial design, stakeholder engagement, and patient recruitment. This provides pharmaceutical companies and contract research organizations with a framework from which to accelerate their investments in rare diseases and better serve the needs of the millions of patients requiring new and better treatments.

1. PhRMA (2021) Progress in Fighting Rare Diseases. Available from: https://www.phrma.org/resource-center/progress-in-fighting-rare-diseases [Accessed 10 November 2021].

Clinical trial landscape

Rare diseases carry a large collective footprint

Rare diseases are so called because of the low number of prevalent patients, with long-standing definitions being fewer than 200,000 people in the US and fewer than 1 in 2,000 people in the EU.[2] Trialtrove assigns a rare classification tag to the diseases, patient segments, and Medical Subject Headings (MeSH) terms that correspond to these epidemiology thresholds. This allows rare patient populations to be readily identified and the broader rare disease clinical trial landscape to be captured. This equates to a total of over 67,000 trials – almost 20% of the entire database. Evidently, while rare diseases are individually uncommon, the combined burden is vast. Orphanet estimates a global point prevalence of 300 million patients, equivalent to around 4% of the world's population.

Within this rare disease clinical trial universe, the dominance of oncology is the major observation, with over 60% of trials designed to improve our understanding of how to treat cancer. Many of the large tumor types count individually towards the wider oncology total, while non-Hodgkin's lymphoma is the single most common disease. One in five of all known rare disease studies are currently ongoing, as trial activity has steadily increased through the last decade. This growth has been relatively evenly distributed across the various trial sponsor types – industry sponsors such as biopharmaceutical and medtech companies steadily account for around half of all rare disease clinical trials.

Figure 1. Rare disease trial landscape

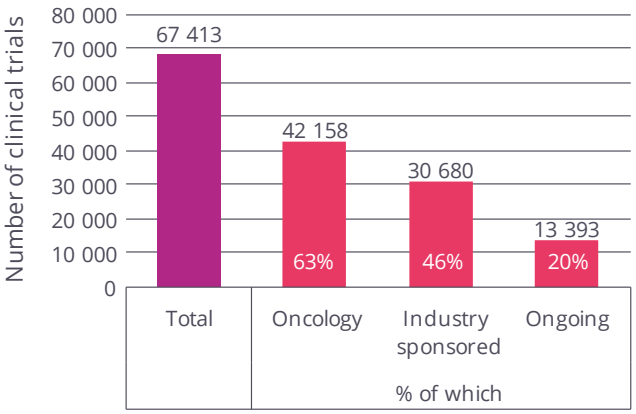


Figure 1 describes these topline segmentations. In order to focus in on a more representative set of rare disease studies, the remainder of this section includes only industry-sponsored trials initiated since 2010, separately evaluating oncology and non-oncology settings. Note that trials classified in multiple therapeutic areas are counted once per therapy area, leading to a slight elevation in total.

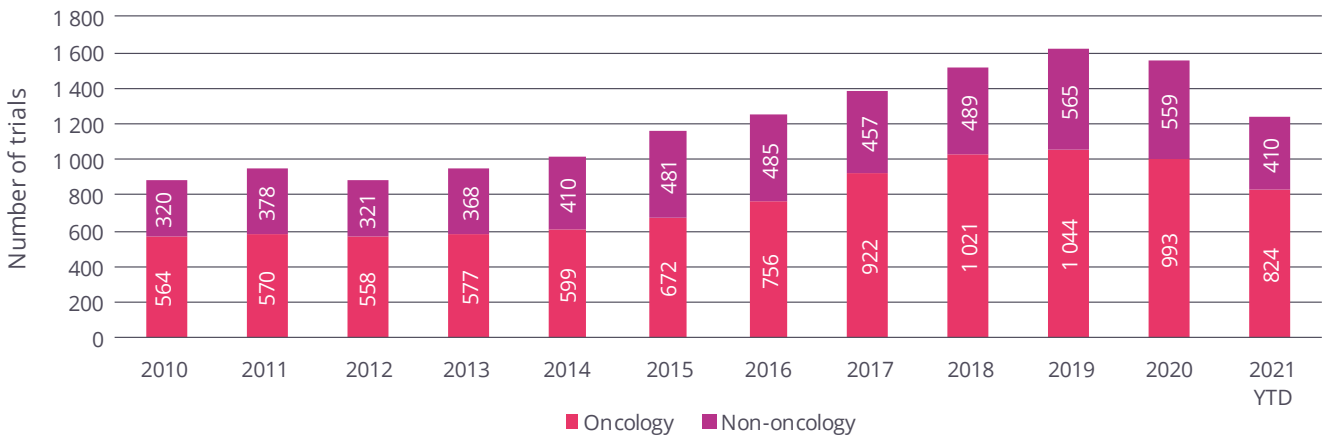
2. National Institutes of Health (2021) FAQs About Rare Diseases. Available from: https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases [Accessed 10 November 2021].
3. Orphanet (2019) 'Rare is not rare'. Available from: https://download2.eurordis.org/pressreleases/PrevalencePaper_JointStatement_170919_Final.pdf [Accessed 10 November 2021].

Industry trial activity is strong and growing

As shown in Figure 2, clinical activity for rare diseases has consistently grown through the last decade, achieving a minimum 5% growth rate every year between 2013 and 2019. In 2010, the biopharmaceutical industry initiated 884 rare disease studies, with the total expanding year-on-year to a peak of 1,609 in 2019. Although there was a slight 4% contraction in the pandemic-affected 2020, similar trends were observed in nearly every other therapy area.[4] Activity through 2021 so far appears robust, although a like-for-like comparison with previous years is not yet possible owing to reporting delays by industry sponsors.

This growth has come from both the oncology and non-oncology rare disease segments. The proportion of oncology studies has remained consistently at 60–65% of the total, indicating the attention on both traditional rare diseases as well as oncology opportunities.

Figure 2: Industry-sponsored rare disease trials by start date, 2010–present



Source: Trialtrove®, October 2021

The rare disease trial landscape follows similar trends to the wider geographic spread of clinical research. The US clearly leads the global development landscape, with just over half (53%) of all rare disease trials involving a clinical site in the US. This is three times higher than the next highest countries – the UK, Germany, and France – which are all closely clustered with around 2,500 trials each since 2010. China is somewhat lower in the list of rare disease trial locations than might be expected considering the size of its addressable patient population. Much of its activity lies within the rare oncology segment, where it is the second most common location, aided by a domestic R&D ecosystem that is heavily targeted towards fast-follower oncology drugs. Outside of oncology, China is down in 13th position, behind countries such as Poland and

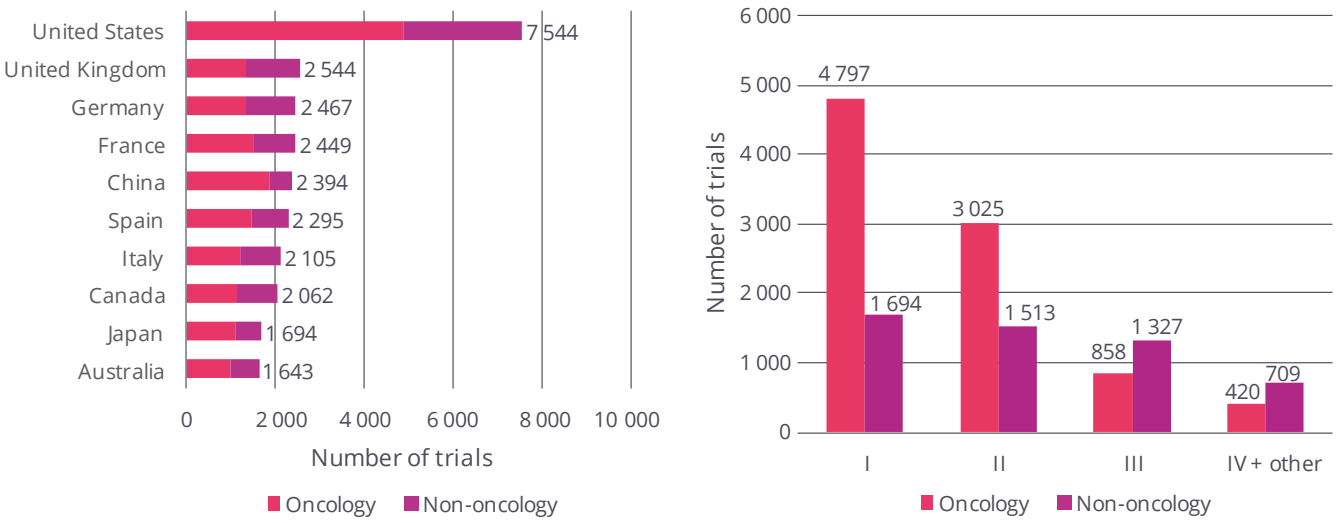
4. Shin D (2021) 2020 Clinical Trials Roundup. Available from: https://pharmaintelligence.informa.com/resources/product-content/2020-clinical-trials-roundup-disruptions-to-the-trial-landscape [Accessed 10 November 2021].

Belgium, suggesting a large untapped opportunity should trial sponsors be able to identify and recruit patients with rare diseases. The remaining countries in the top 10 list of locations for rare disease trials are all mature markets: Spain, Italy, Canada, Japan, and Australia.

Tallying the number of trials by phase reveals an interesting dynamic for the non-oncology rare diseases. Each of the main stages of drug development – Phase I, II, and III – has seen approximately 1,500 clinical trials since 2010, without any notable drop-off for later stages of drug development due to the attrition of drugs in the pipeline as clinical trials fail. Rather, the large number of Phase III trials for non-oncology rare diseases points towards the incentivization of research by governments and regulators, as well as the greatly improved clinical development success rates for rare diseases. A recent analysis by Informa Pharma Intelligence and the Biotechnology Innovation Organization (BIO) shows that rare disease drugs carry a threefold higher likelihood of approval compared to drugs for high-prevalence chronic diseases.[5]

Distribution within the rare oncology segment is as expected, with the majority of clinical trials at the Phase I and II stages. Uniquely with oncology, there is also a sizable number of Phase I/II trials, typically reserved for basket trial designs whereby multiple different indications are studied in a single trial. This evaluates potential efficacy signals across a range of patients, before expansion cohorts are initiated either within the same trial or in a new Phase II study. Such trials that bridge two clinical phases are counted at the lower stage of development in Figure 3.

Figure 3: Snapshot of industry-sponsored rare disease trials by location and phase, 2010–present



Source: Trialtrove®, October 2021

5. Informa Pharma Intelligence (2021) Clinical Development Success Rates and Contributing Factors 2011–2020. Available from: https://pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/2021/files/reports/2021-clinical-development-success-rates-2011-2020-v17.pdf [Accessed 10 November 2021].

Rare disease clinical trials are primarily sponsored by large pharmaceutical companies, as shown in Table 1. The total count is comfortably led by Bristol Myers Squibb with a total of 942 trials since 2010, with a heavy focus within cancer. Novartis, Roche, AstraZeneca, and Merck & Co complete the top five, both in terms of overall studies (>500 each) but also specifically within rare oncology (>400 each). A large oncology portfolio is therefore critical to being a broad rare disease leader.

Sanofi has sponsored more traditional rare disease trials than any other company since 2010, due to the historical activity of acquisitions such as Genzyme and Bioverativ. Takeda is similarly highly ranked through its acquisition of the rare disease specialist Shire, while the remaining leading pharma sponsors have built their presence through a mix of internal R&D and smaller M&A deals. In general, a strong focus on non-oncology rare diseases tends to come at the expense of a leading rare oncology portfolio, although Novartis is the one exception that invests heavily across both areas.

Table 1: Top 10 sponsors of rare disease clinical trials, 2010–present

	Total trials	Total rank	Oncology trials	Oncology rank	Non-Oncology trials	Non-Oncology rank
Bristol Myers Squibb	942	1	869	1	73	12
Novartis	670	2	462	3	208	3
Roche	639	3	497	2	142	7
AstraZeneca	538	4	416	5	122	8
Merck & Co	535	5	457	4	78	11
Johnson & Johnson	443	6	272	6	171	5
Takeda	433	7	247	8	186	4
Pfizer	424	8	263	7	161	6
GlaxoSmithKline	405	9	189	11	216	2
Sanofi	368	10	142	15	226	1

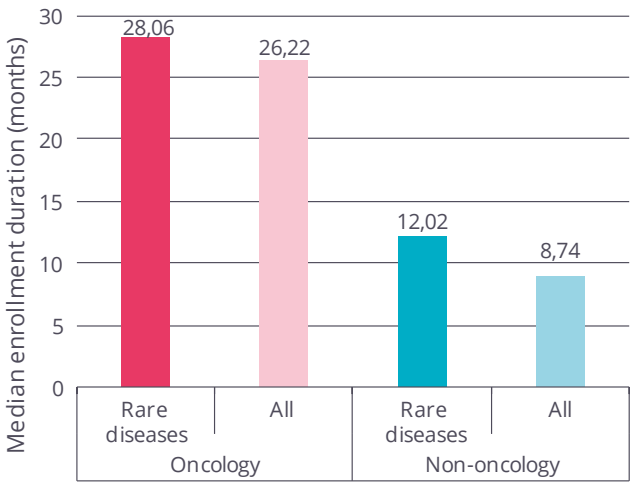
Source: Trialtrove®, October 2021

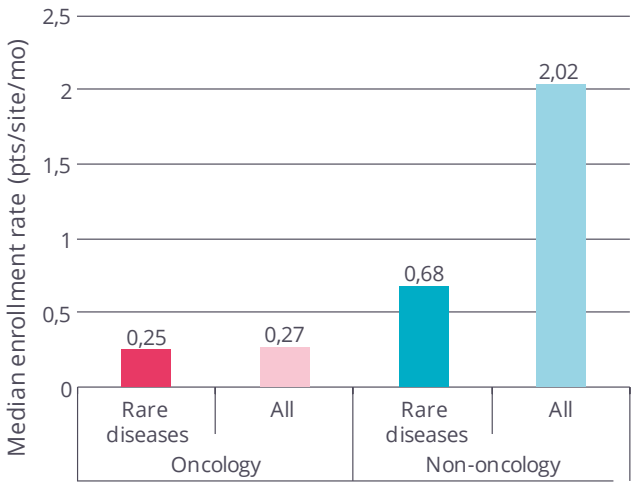
Studies for rare diseases typically take longer to recruit and conduct

Owing to the initial challenge of diagnosing rare diseases, it is unsurprising that clinical trials for these patients typically enroll at a slower rate. This is most pronounced for non-oncology rare diseases, where a clinical site enrolls a median of 0.68 patients per month, which is three times slower than the average across all non-oncology diseases (2.02 patients/site/month). As a consequence, the enrollment duration of rare disease trials is typically longer, which adds to the cost burden of rare disease R&D.

The distinction between rare oncology and general oncology is less apparent, although this reflects the fact that many highly prevalent oncology diseases are also technically rare according to the standard definitions. By comparison, rare and general oncology trials have much slower enrollment rates and longer enrollment durations due to the narrow period of time in which patients may be eligible. These benchmarks are shown in Figure 4.

Figure 4: Enrollment rate and duration benchmarks for rare and conventional diseases



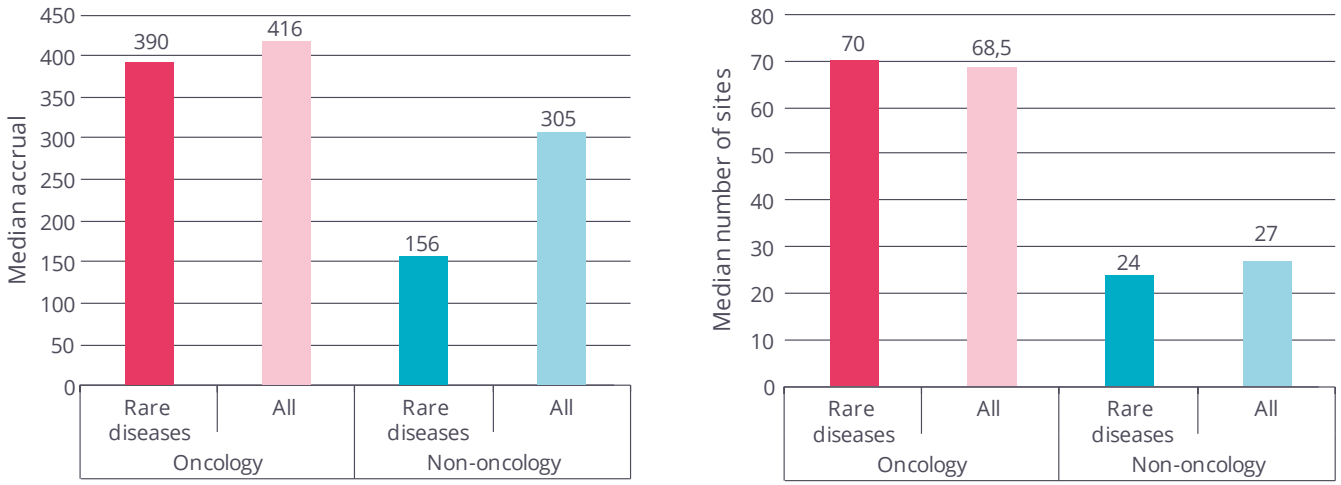


Source: Trialtrove®, October 2021

Traditional clinical research remains heavily centralized around the investigational site. To compensate for the sparse eligible patient numbers and slow enrollment benchmarks for rare diseases, clinical trials either require a larger number of clinical sites, or simply recruit fewer participants. A larger number of sites adds additional complexity, burden, and cost to each study, while conversely smaller sample sizes limit the statistical strength of the results. A cross-section of industry-sponsored Phase III trials conducted since 2010 in Figure 5 shows that non-oncology rare disease trials typically accrue 156 patients per study, which is just half the number (305) for all non-oncology trials. Rare disease drug developers are therefore prioritizing keeping R&D costs down, supported by greater flexibility at the regulatory review stage.

Again, for the oncology subset, there is relative parity between rare diseases and all oncology trials. Sample sizes are higher across all Phase III oncology trials, averaging at approximately 400 patients, although in order to achieve this a median of approximately 70 investigational sites are required for each study.

Figure 5: Phase III cross-section of patient accrual and number of clinical sites for rare and conventional diseases



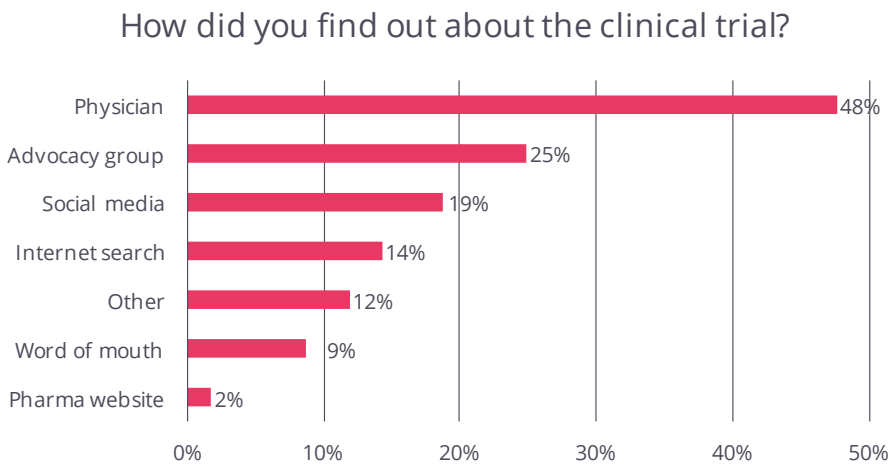
Source: Trialtrove®, October 2021

Rare disease patient perspectives

Survey reveals important considerations for sponsors

To gather insights into the clinical trial experience for patients with rare diseases, Informa Pharma Intelligence partnered with the advocacy group Rare Patient Voice. A total of 1,800 people were contacted via email in early 2021 and invited to participate in an online survey that gathered opinions on participation or intent to participate in clinical trials.[6] Over 900 patients participated in the survey, providing a base of information on clinical trial behavior attitudes, needs, and demographics. Their views provide key insights into public perception of clinical trials, based on both retrospective experiences and potential future participation. The following 10 important messages from trial participants can be distilled from the study's findings.

1 **Trial participation is most frequently the result of a physician referral.** Almost half of all participants sourced their clinical trial through this channel – eclipsing all other sources by some margin, and emerging as more than twice the proportion who had used ClinicalTrials.gov (see #2).

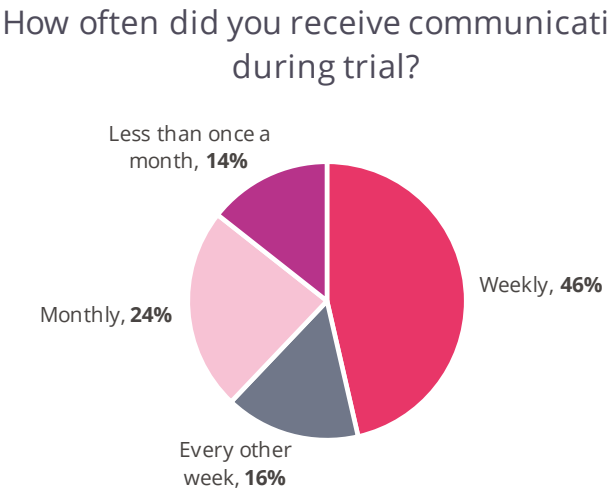


2 **ClinicalTrials.gov had not been used by about three in every four trial participants.** Use of this resource was particularly low among those aged 65+ years. However, when usage was evident, it was highly rated – attaining an average score of 4.1 out of a maximum score of 5, contrary to other findings on ClinicalTrials.gov usage. This rating suggests that the website is performing well, but with room for improvement.

6. Informa Pharma Intelligence (2021) Patient Perspectives on Clinical Trial Participation Report. Available from: https://pharmaintelligence.informa.com/resources/product-content/2021/07/22/16/07/patient-perspectives-on-clinical-trial-participation-report [Accessed 10 November 2021].

3 **A majority of trial participants rate the enrollment process highly.** Two-thirds move from prescreening to enrollment within a week, with this speediness yielding an average rating of 4.2 out of a maximum score of 5. An impressive 80% viewed the process positively, suggesting that the mechanisms of screening and subsequently enrolling are working with efficiency and effectiveness.

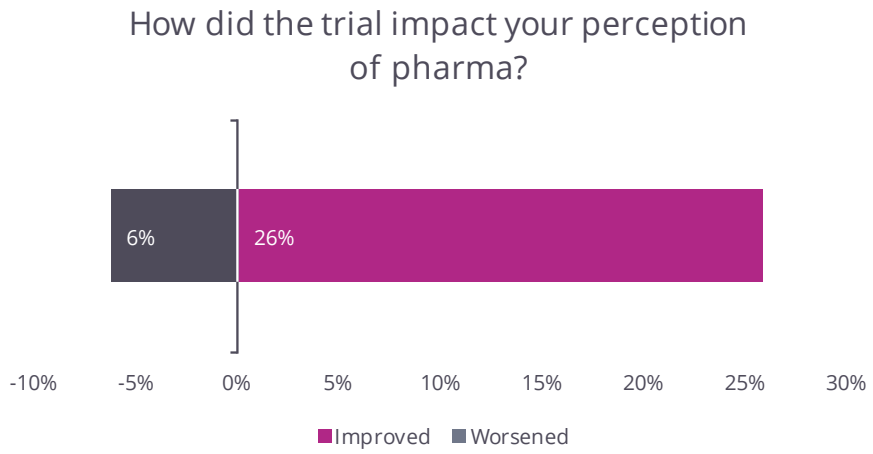
4 **Communication is well pitched.** 86% of trial participants felt that the level of communication they received during their trial was sufficient. This was typically around the once-a-week mark, a frequency eliciting the very highest levels of satisfaction, and one which suggests that – in the minds of participants – this is the most desirable level of communication during trials.



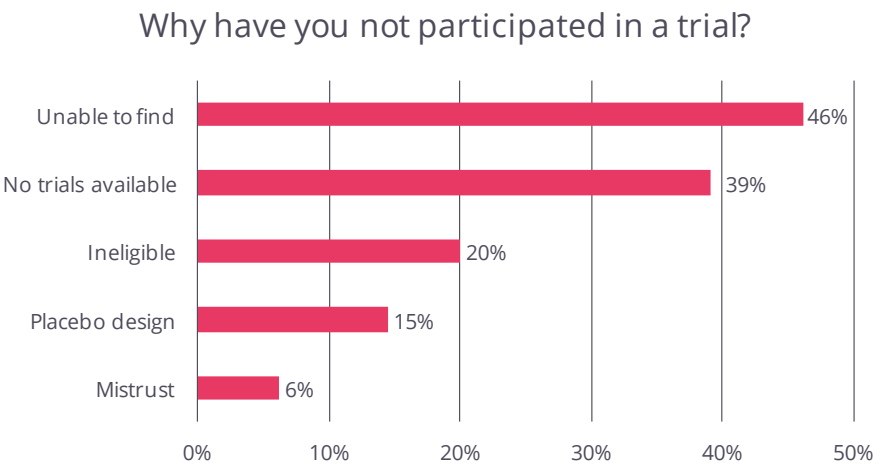
5 **Receiving trial results is clearly seen as important.** However, over 60% of clinical trial participants had not received the results of the study in which they participated. This was a figure clearly at odds with the expectations of a majority of both trial participants and non-participants. Here, the message was very much along the lines of "if we participate in a trial, we would like the results, please." Indeed, a need for more trial feedback emerges as the number one suggested change to the clinical trial experience.

6 **A majority of trial participants would both recommend and repeat the process.** Over 80% of those who had already participated in a trial – often in the context of a positive overall experience – would happily participate again and would recommend participation to others. Their motivation is often selfless, with a desire to help others and to assist in the advancement of more effective treatments and cures. Accompanying benefits include financial compensation and additional knowledge, but these are clearly eclipsed by more altruistic intentions.

7 **A minority of negative overall trial experiences damage perceptions of the pharmaceutical industry.** The message is very much that a poor trial experience worsens views of the industry. For every four participants with a positive trial experience that raises their impressions of pharma, a fifth patient will become a detractor, despite best intentions.

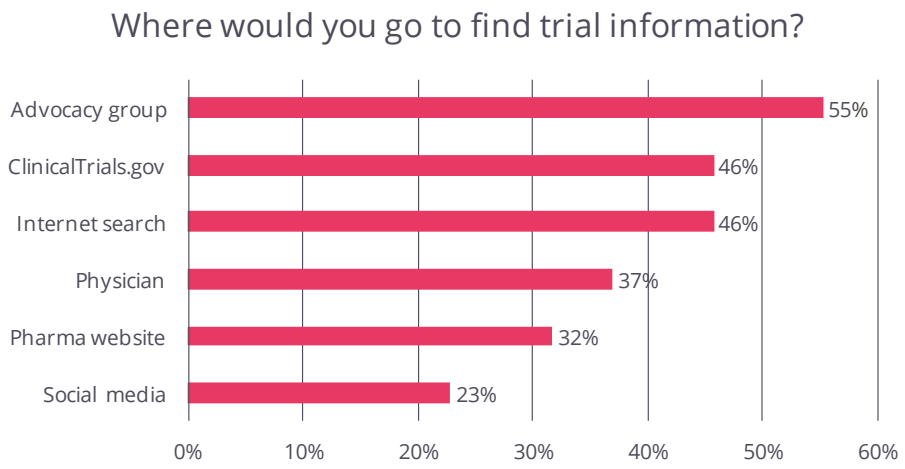


8 **Being unable to source relevant trials typically prevents participation.** The most prevalent obstacles to participation are undoubtedly being unable to locate relevant trials that are an appropriate match to both geographical location and/or condition/disease. Accompanying comments from non-participants provided insight into the enrollment difficulties experienced by some, such as not hearing back from the trial site.



9 **A majority of non-participants in each demographic category were willing to participate in a clinical trial.** This was a finding particularly emphasized if their physician was making a referral. Over 80% indicated that physician referral would spur their participation – clearly highlighting the power of physicians in driving participation.

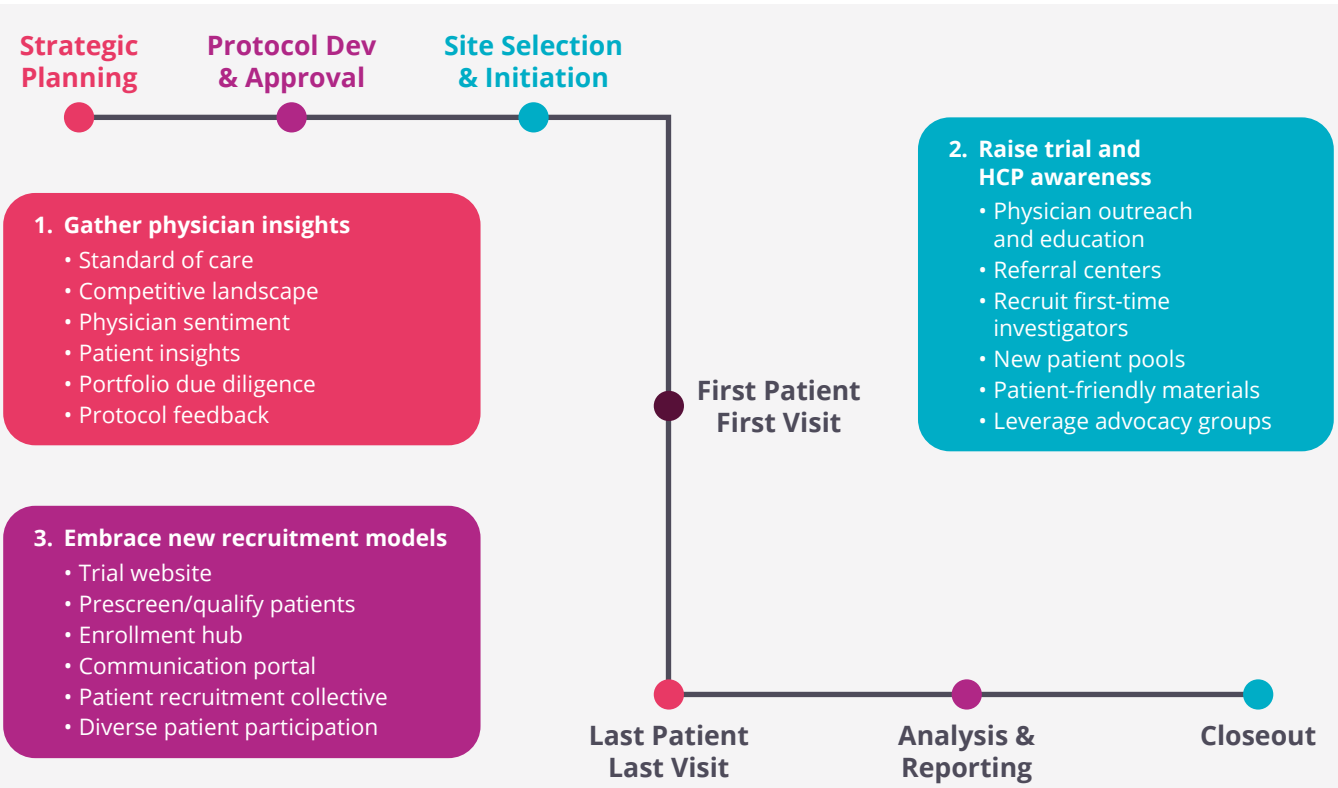
10 **A disease/patient advocacy group website emerged as the number one method of sourcing clinical trials information.** For patients who have not yet participated, most would gather information about clinical trials from advocacy group and disease-specific websites.



Strategic recommendations for trial sponsors

From rare disease clinical trial benchmarking and patient insights into the clinical trial process, Informa Pharma Intelligence can make a series of strategic recommendations for sponsors of rare disease clinical research. This set of best practices will help sponsors gather insights from clinical experts to design patient-centric studies, build trial awareness among important physician and healthcare professional (HCP) groups, leverage advocacy groups to speed up patient recruitment, and ultimately gain a competitive edge in rare disease trial strategies. These are described in Figure 6, with further detail in each subsequent section.

Figure 6. Study progress and rare disease best practices



Gather insights from clinical experts to design patient-centric studies

Informa Pharma Intelligence's survey in collaboration with Rare Patient Voice shows the essential role of physicians in rare disease clinical research. Physician referral is by far and away the most common route to study participation, while physicians also are a common source for trial awareness and information. Physicians can also play a pivotal role in the trial design process, being much closer to the disease in question and patients' unmet needs. With rare diseases in particular, there is comparatively little information on traditional inputs that inform study design,

such as patient availability, treatment practices, and clinical endpoints. The HCP outreach and engagement services provided by Citeline Engage are crucial to access these insights, which in turn facilitate the planning and execution of successful clinical trials.

At the trial planning stage, primary research and focus groups allow for the rapid creation of a consensus view, which is not otherwise available for underserved rare diseases. Physicians can offer important on-the-ground information on current standard of care, competitor positioning, and treatment guidelines. Physicians are also a gateway into patient insights and unmet needs. From a strategic point of view, physician and key opinion leader insight can guide the creation of a target product profile, which is a vital document to align multifunctional internal stakeholders around overall development goals, or to conduct due diligence for potential external therapeutic opportunities.

Transitioning into protocol development and study feasibility, physicians and clinical experts remain essential partners. For a clinical trial to produce highly relevant data, physicians are well placed to advise on eligibility criteria, comparator arms, and endpoint selection, all designed to reduce burden and increase patient centricity. Study protocols must be critiqued and stress-tested in order to minimize potential costly amendments further down the line.

Build trial awareness among key stakeholders from the outset

Once the protocol is finalized and approved, attention must turn rapidly to raising trial awareness and investigator activation. These external activities must happen in concert with traditional feasibility and site selection processes in order to smoothly transition into patient enrollment. For any rare disease program, successful trial awareness should have a multi-pronged approach that targets the important stakeholders: physicians, investigators, and patients themselves.

As previously detailed, around one in two surveyed patients with a rare disease who participated in a trial did so as a result of physician referral. A vast majority of patients think it is important that HCPs are aware of studies being conducted in their community, according to a study from the Center for Information and Study on Clinical Research Participation (CISCRP).[7] Rare disease trial sponsors should therefore prioritize outreach strategies to physicians as they are essential allies for raising trial awareness. In spite of the vital role physicians play, current engagement is far from optimal as clinical trial options are rarely discussed during patient visits.

When engaged and consulted, physicians and other HCPs can be more than just advocates for clinical trials – they can also be potential investigators themselves. For rare diseases, where established investigators with large referral networks may be in short supply, study sponsors should always be nurturing the next generation of investigators with every engagement. Expanding clinical trial networks through first-time investigators opens up new pools of patients and referral centers. Just as it is necessary to

7. Anderson A, et al. (2018) Global Public Attitudes About Clinical Research and Patient Experiences With Clinical Trials. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2705849 [Accessed 10 November 2021].

understand the barriers for patients to participate in trials, it is equally useful to address the hurdles that prevent HCPs from becoming investigators.

Recognizing the growing influence of patient organizations and disease advocacy groups, particularly within the rare disease universe, any trial awareness strategy also needs a patient-focused component. This can be as simple as developing patient-friendly materials and a website presence, rather than relying upon a ClinicalTrials.gov entry that may be difficult to understand. Advocacy group websites are the number one resource for patients who have not yet enrolled in a trial, second to general internet searching, as revealed by the Informa-Rare Patient Voice survey. Trial awareness among patients, whether direct or through support networks, is central to any successful rare disease trial as it begins enrolling.

Embrace new end-to-end recruitment models

Recruitment and trial awareness are inextricably linked, such that best practice activities to raise awareness among investigators and patients will support a fast start to enrollment. On the patient side, resources including targeted websites dedicated to ongoing studies can also provide prescreening services, supplying eligible participants who can be triaged towards individual clinical sites. These same resources can be adapted to incorporate HCP-facing components to aid in wider education and discoverability.

There are several benefits to a centralized approach to awareness and enrollment rather than delegating responsibilities to study partners. A single hub can be used to track patient interest, eligibility, and referrals through the system, allowing for real-time monitoring of recruitment channels and site performance. While patients may not meet eligibility criteria for the study in question, analysis of screen-outs can be used to inform future study designs, or indeed introduce protocol amendments if necessary. This hub can also double as a communication portal, encouraging email signup that allows sponsors to reach the right cadence of communication to trial participants. Regular updates with regard to study progress aid patient engagement and retention within the study, supporting an overall positive trial experience. This includes post-trial communication such as study results, an often overlooked step that satisfies a primary motivation for rare disease patients to participate in clinical trials – to advance the science and benefit patients in the future.

Lastly, an innovative recruitment model is emerging that is particularly relevant for rare disease studies owing to the disparate geographic spread of patients and importance of advocacy groups. Citeline Connect is pioneering the patient recruitment collective, bringing together a diverse range of patient-facing organizations from traditional recruitment partners through to disease awareness organizations, patient advocacy groups, pharmacies, and even diagnostic service providers. By creating and tapping into a network of validated partners that can steer patients in the direction of clinical trials, study sponsors can cast the net far wider and more equitably. This one-to-many approach has substantial advantages over working with select traditional recruitment partners, which have failed to address the lengthy enrollment period of rare disease trials and reinforce a lack of diverse participation.

About The Author

Daniel Chancellor

Thought Leadership Director, Informa Pharma Intelligence

Daniel has a decade of experience as an analyst in the biopharma industry, spanning roles in drug discovery, market analysis, competitive intelligence, and strategic consulting.

He now develops and leads Informa Pharma Intelligence's Thought Leadership program, producing materials that help clients across a range of hot topics in the biopharma industry. As part of this, Daniel regularly participates in webinars, conferences, and other speaking arrangements, and he has been featured across leading publications such as Nature Reviews Drug Discovery, Fortune, Scientific American, Scrip, In Vivo, and Vice.

Prior to joining Informa, Daniel worked as a medicinal chemist at the UK biotech company Summit Therapeutics and graduated with First Class Honours in Natural Sciences from the University of Bath.

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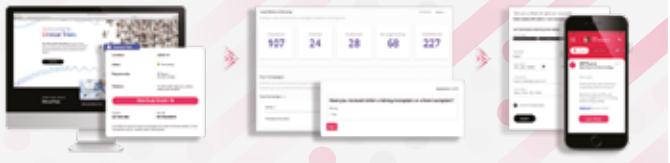

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Accurate and timely intelligence about the drug development pipeline is vital to understanding the opportunities and risks in today's biopharmaceutical marketplace—whether you are targeting an unmet medical need, investigating promising new therapies or researching drug development historical trends and treatment patterns. If you are providing contract research or other services in the pharma industry, you need to stand out. A solid understanding of your potential clients' pipelines and competition will help you leave a lasting impression.

Contact us at pharma@informa.com

United States
605 Third Avenue
Floor 20-22
New York
NY 10158
USA
+1 908 547 2200
+1 888 670 8900

United Kingdom
Blue Fin Building
110 Southwark Street
London
SE1 0SU
United Kingdom
+44 20 337 73737

Japan
21st Floor, Otemachi
Financial City North Tower
1-9-5, Otemachi
Chiyoda-ku
Tokyo
100-0004
+81 3 6273 4260

China
23rd Floor
16F Nexxus Building
41 Connaught Road
Hong Kong
China
+85 239 667 222

Australia
Level 4
24 York Street
Sydney
NSW, 2000
+61 (0)2 8705 6968