CLARINESS

Overcoming clinical trial delays and accelerating clinical trial set-up and enrollment

How Europe's leading patient recruitment platform, ClinLife, accelerates study enrollment

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Introduction

Patient recruitment is still considered by sponsors, CRO's and research sites as the biggest challenge to the successful development and marketization of new therapies and medications, as was highlighted in our latest whitepaper. Although in recent years an increasing number of third-party providers have started offering patient recruitment services, most of these lack the expertise that ensures the quick start of recruitment and on-schedule completion of the study.

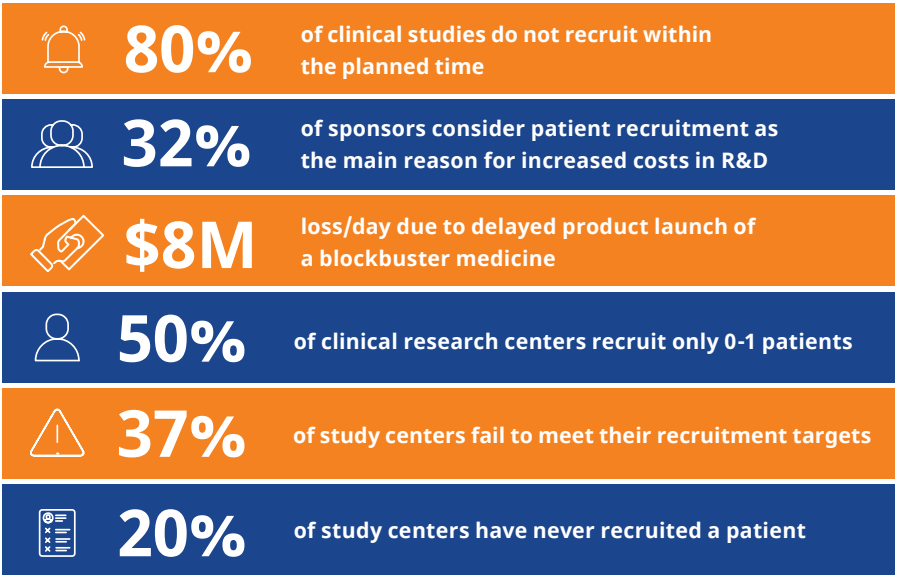
Despite the increasing focus on patient recruitment, study delays are in fact increasing.

- Since March 2021, around 1,000 organisations supporting clinical trials as a sponsor, collaborator or contract research organisation (CRO) have announced **disruptions to planned and ongoing clinical trials,** as reported by Clinical Trials Arena"

- Already before the COVID-19 crisis, **50% of all clinical trials needed to extend the recruitment phase** due to poor results, with **70% of the studies failing recruitment targets altogether** - as reported in the journal Trials 2020.

- Recent data analysis suggest that **study timelines have doubled** beyond planned enrollment periods due to low recruitment rates, as reported in Drug information journal

- Delays in the start of recruitment for studies costs **sponsors between $600K and $8 million in lost marketization**, according to a recent report by Forbes



The importance of getting clinical trials set-up quickly

The start-up phase of clinical trials is one of the most costly, resource intensive and prone to delays area of drug development as noted, among others, by Carolann Schimanski in Applied Clinical Trials. Despite increasing awareness of the importance of a quick set-up and start of recruitment in order to prevent delays – delays in a phase III trial costs a sponsor between $12 and $15 million depending on therapeutic area and complexity - around **86% of clinical trials are delayed in the set-up phase** and can't start enrollment as planned.

The difficulties with setting-up and starting clinical trials have a variety of reasons that in the past years have been an increasingly topic of study for experts. In the end of 2021, Jennifer Lai et al published a largescale overview study called "Drivers of Start-Up Delays in Global Randomized Clinical Trials" in *Therapeutic Innovation & Regulatory Science*, that examined some of the most common reasons for delay. Together with our 17+ years of experience in which we successfully supported over 1200+ global clinical trials in a variety of indications, we have prepared this overview of **the 4 most common delays.**

1. Complexity of study procedures and protocol

One of the main reasons for delays in the start-up phase of clinical trials is the complexity of the protocol designs and assessments, but also the increasing degree of globalization of clinical trials. Trials often involve sites in different countries and continents with different time zones and cultures, but also with different regulations for conducting research and recruitment, and with local standards of care.

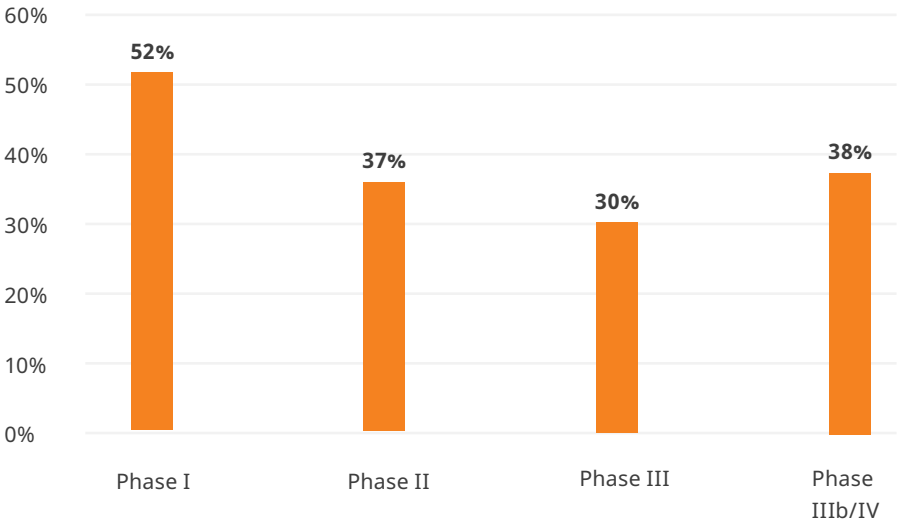
A 2016 analysis of clinical trial set-ups by the Tufts Center for the Study of Drug Development, found that **"57% of protocols had a substantial amendment, with nearly half of these considered "avoidable".**

Given the substantial cost of protocol amendments, estimated at about $141,000 for a phase II trial and about $535,000 for a phase III trial, and the fact that these modifications often result in fewer patients actually being screened and enrolled compared to trials that run on time without protocol amendments, this is an area that trial organizers need to pay particular attention to. One way to do so, is using a third-party vendor with experience and data in study feasibility research, like Clariness.

Of the 6,855 protocol amendments that happened **before the enrollment phase** had started, the three common protocol changes researchers identified were related to the "description and eligibility criteria of the patient population under investigation", "the number and types of safety assessment procedures" and "edits and revisions made to the general study information".

The most common reasons for study amendments **after the enrollment period had started** are "regulatory requests, new safety or dose related information about the study drug, new standards of care and wrongly estimated patient recruitment targets". Especially the later, can be easily be prevented by data-driven feasibility analysis and the review of the protocol by recruitment experts.

Proportion of protocol amendments occuring before the first patient has received the dose (Getz et al)

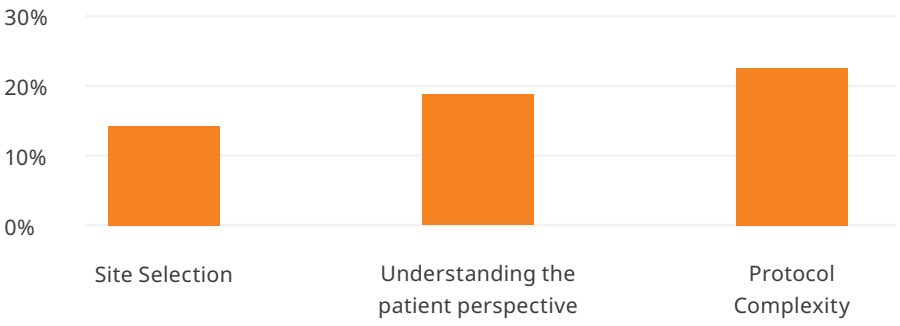


2. Poor feasibility analysis & understanding of local patient population

At Clariness, we are often approached by sponsors or study organizers who need help "saving" their enrollment campaign that is failing the recruitment goals. As we notice, and is also highlighted by analysis by independent researchers, failures to reach enrollment goals often result from **poor feasibility analysis of the local patient population and sites.**

For example, estimates of how many patients can be recruited from a local patient population are often based on poor analysis or even assumptions that patients are likely to join simply because there are limited treatment options available or, in the case of healthy volunteers, because there is a high compensation for participation. With high competition between organizers on a small pool of patients who are likely willing to join on these grounds alone, this is not enough to make enrollment a success. Hence, researchers call for trial organizers to invest more in feasibility analysis and base their assessments and protocols on real data instead of assumptions.

Major challenges to setting up effective patient recruitment strategy according to sponsors, sites and CRO'S (n=812)



At Clariness we make a feasibility analysis based on the protocol and selected sites. Having successfully supported over 1,200 clinical trials and worked with over 7,000 sites globally, we create a data-driven outreach strategy.

1. Data gathered via **our site analysis and online patient surveys** provides a **market-focused approach** for a better barometer of patient eligibility and site potential. We for example analyze the trial protocol draft and make suggestions based on our knowledge of the local patient population, thereby making the likelihood for required amendments for the study population lower.

2. Our data analysis tools to help **assess site capabilities**, uncover potential problem areas in your protocol, determine how many sites are needed for timely completion, and identify the best regions for your study to avoid costly delays in bringing products to market.

Learn more about Clariness' feasibility analysis here

3. Slow set-up and site activation delays

The saying that a "good beginning is half the task" is especially true for clinical trials. Recent studies and reports highlight how the set-up of a trial and specifically the time from protocol finalization (PF) to first patient in (FPI) is an "important indicator of a trial's success", specifically in the recruitment. With a new clinical trial on average taking between 6 to 8 months from receiving a protocol to activation of the trial and potential enrollment of the first patient, it is crucial that sites are activated quickly and early to begin recruitment.

*"Clinical study start-up is a key determinant of success in a clinical trial, and **the time required to activate a trial may be inversely related to its enrollment rate.** In order to begin recruitment, sites need to be qualified, gain regulatory approval, including IRB/ethics committee approval, and receive training."*

Jennifer Lai et al "Drivers of Start-Up Delays in Global Randomized Clinical Trials", in: Therapeutic Innovation & Regulatory Science, volume 55, pages 212–227 (2021)

While an early start is important, the authors note that it's important to understand that even "a minor error on a critical document such as an informed consent form [..] present a significant set-back as the site may not be able to enroll participants until the error is corrected."

We have successfully a **98% approval rating on first submission from EC/IRBs** around the globe. Having successfully supported over **1,200+ studies** and worked with **7,000+ sites** in **40 countries,** including **750 sites in Germany alone**. We can support you from setting up the patient-friendly materials and getting EC approval, to creating study landing pages on our ClinLife Portal. Enrollment can start within 2 weeks of contract signing.

Request Information

4. Bad tracking and accountability

Ultimately, even when sites are activated quickly a common problem is that they fail to recruit patients, sometimes simply because they fail to answer interested patients. While these problems can be prevented partly by conducting a **comprehensive feasibility and optimization study of each site,** not only in terms of the ability to conduct the trial but also to recruit and retain patients and compliance with local regulations, it can still occur because of other reasons.

The often cited statistics from the Tufts Center for the Study of Drug Development that some **27% of investigator sites are unable to enroll a single qualified patient,** or that up to a **third of all referrals are never contacted,** or contacted to late, show that sponsors don't take into account that this can be easily improved by giving sites the right tools to handle referrals. As sites often lack tools and digital literacy in dealing with complex, secure systems for processing patient data, as well as time to learn how to use these, we at Clariness believe that a good onboarding and tracking tools can help sites achieve their recruitment goals.

We onboard sites quickly through eay-to-use resources including patient pre-screening tools, site tracking and readiness tools, and support kits for patient engagement. This Investigator Service furthermore ensures that patient data is stored safely and anonymously, following the strict European data protection regulations.

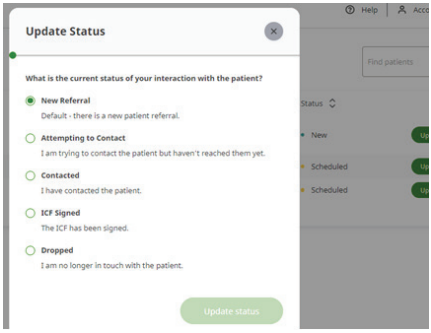


Figure 1. Clariness' innovative Investigator Service enables sites to easily track referral status in a secure digital environment. Sponsors get direct insight in site performance through personal reports and a sponsor portal.

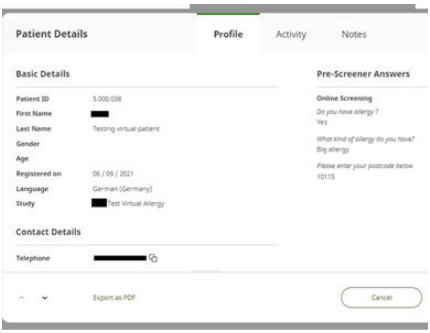


Figure 2. Giving insight in the pre-screener answer of patients allow sites to decide to invite the patient for on-site screening or not, reducing workload.

The need for innovative enrollment strategies that can overcome trial delays

As delays in clinical trials are most often connected to delays to patient recruitment campaigns, it remarkable that studies show that about 32% of all sponsors, sites and CRO's still do not have dedicated patient recruitment and retention strategies. As Mary Jo Lamberti et al conclude in their article "Benchmarking Patient Recruitment and Retention Practices" the "most widely used recruitment tactics are traditional" and rage from "physician referrals (16%), newspaper advertisements (16%), and radio advertisements (13%)".

These **traditional recruitment campaigns are very vulnerable to delays in other parts of the trial process** as they can not easily be adjusted once underway or put on hold temporarily when protocol amendments are necessary or when sites have problems getting activated or have no screening capability; more so when sites take a long time to set-up between receiving EC-approval and getting campaigns out to patients.

Nayan Chaudhari concludes in Perspectives in Clinical Research (PICR) 2020 that "Awareness of proven [recruitment] challenges and review strategies" is one of the most important ways trial organizers can "optimize recruitment to facilitate drug development". Hence, even FDA Commissioner Dr Scott Gottlieb in 2021 called for sponsors to look for more non-traditional and innovative ways to reach, engage and enroll patients.

ClinLife Registry, an innovative patient portal to accelerate study timelines & enrollment

With the launch of ClinLife Registry, the indication-specific patient recruitment platform, Clariness looked to offer new innovative ways to connect organizers of clinical trials with patients.

Supporteed by the European Investment Fund, the ClinLife platforms are Europe's largest, patient-friendly platforms.

Using an **indication-based marketing approach** to reach patients over 40+ possible channels, ClinLife Registry recruitment can start **within 2 weeks** of signing of the contract as no additional EC-approval is needed. In some recent cases, this meant that patients were **randomized within one week.**

While there are several existing clinical trial registries, such as Clinicaltrials.gov or the German DRKS (Deutsches Register Klinischer Studien), these have an outdated design and difficult-to-navigate web pages and forms. More so, the study descriptions are written in complex medical terminology that is only accessible to experts and the study pages even lack easy contact options for patients to sign-up for a study.

Comparing traditional recruitment methods

Doctors/study centers

- Direct access to patients
- Established relationship & trust
- Limited patient pool, quickly exhausted
- Fully dependent on pro-active actions of doctors

Offline recruitment

- Limited scalability, inflexible
- Not targeted to specific groups
- One way communication
- No direct interaction with patients
- Possible wide reach but no accountability

State databases (clinicaltrials.gov)

- Limited patient pool
- Databases are quickly outdated
- No direct interaction with patients

Digital Recruitment + Registry

- Almost unrestricted access to patients
- Daily updated and targeted approach possible
- Direct interaction with patients possible
- Patient-centric platform and direct database contact

How ClinLife Registry can overcome delays by accelerating recruitment in 2 steps:

No additional EC-approval needed: Typically, most patient recruitment vendors only develop study-specific materials, which require approval from both the client and regional ethics committees (EC), resulting in a long review process of weeks if not months. With ClinLife Registry, we use indication-based marketing, only showing study-specific information after patients completed the digital pre-screener. Hence, enrollment can start within 2 weeks of the contract signing while for example the study-specific materials are still under review.

Diversified patient outreach: Besides paid social media advertisements, ClinLife Registry makes use of over 40+ channels for indication-specific outreach. Based on the study protocol and our knowledge of the local patient population we create an outreach strategy that can include:

1. **Organic search results (SEO):** Our indication-specific landing pages contain lay-friendly information about clinical research, the rights of participants and potential benefits and risks. Patients searching online for health information come across the study page, complete the pre-screener and get shown a list of studies in their proximity that they can participate in. Our call center furthermore answers any questions related to participation that patients might have.

2. **Patient database:** A rapidly growing database with over 50,000 subscribers in the DACH-region alone, advertisement can start immediately, while being fully compliant with local data regulations as the DSVGO in Germany or European Union-wide GDPR.

3. **Partnerships:** Through the platforms of a large number of prominent German patient organizations as well as health apps and health information websites, patients looking for information come across ClinLife, find studies or sign either up for the ClinLife patient database and get contacted when new studies are put online.

4. **Collaborations:** Similarly, to partnerships, the patient team of ClinLife can engage in specific collaborations with social institutions to connect patients to studies.
   In a recent recruitment campaign for a paediatric trial, we worked together with child-care providers to connect interested parents with children to the study.

ClinLife Registry works with patient organizations, health apps, and news websites to connect patients with relevant information and clinical trials

What sponsors & sites say

ClinLife facilitates a direct connection between sponsors, sites and patients, by bringing them together in one patient-centric online-platform. ClinLife has been used by 13 of the 15 largest pharmaceutical companies in the world and some 7,000 sites, of which 850+ sites in Germany alone.

What sponsors say:
"The combination of recruitment via Clariness' online ClinLife platform and pre-screening has proved to be a very valuable tool for effectively monitoring, directing, and controlling patient referrals to investigator sites. The high quality of patients referred has resulted in many randomizations and a major reduction in screening efforts at the sites."

Clinical Research Study Leader, headquartered in Switzerland

What sites say:
"We love the Investigator Portal. We prefer it over any of the other screening options, because you [Clariness] do the pre-screen and get a lot of information for us, before we contact them. It really helps us as we're a tiny department that does a lot, so anything that helps is appreciated."

Rebecca Wirth, Clinical Research Center at Miami Valley Hospital (USA)

Learn more about ClinLife Registry here or **Contact us here directly**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