Tricks of the Trade:

Recruitment and Retention Planning for Different Study Types

Focus on Chronic, Acute, Rare and Geriatric Programs

By: Melynda Geurts, M.S.

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PATIENT RECRUITMENT SERVICES
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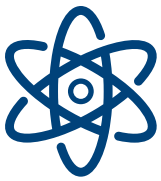
About this ebook:

In an effort to raise the bar for medical advancement, clinical trials are growing increasingly complex. Addressing the unique perspectives of patients, site coordinators, investigators, sponsors and the FDA add to the complexities and can lead to delays in enrollment.

In this ebook, we'll examine important factors to consider when planning recruitment and retention in clinical trials and review the development, execution and results of four trials.



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Part 1: Setting the Stage

In this section we'll take a quick look at clinical studies through the eyes of each of the stakeholders in study success.

Chapter 1:
The Increasing Complexity of Clinical Trials—Viewpoints

Viewpoints

Clinical trials involve five main stakeholders, and each group has its own views and motivations. Here is what people in those groups are saying about clinical trials from their own perspectives:

Patients

Most patients (69 percent) said they have not participated in a clinical trial because they were not made aware of any trials.

This tells us that our industry needs to do more to educate the public about clinical trials. Too many people are unaware that it's an option for them. This is likely the reason why recruitment tends to be the number one reason studies do not finish on time.

Site Coordinators

Among site coordinators, 28 percent said that inclusion/exclusion criteria has the single biggest impact on patient recruitment success.

How can we put a program into place that can help sites expand their database and their reach?

Investigators

Most investigators (76 percent) said that they are involved in the right amount or too many clinical trials.

There are competing trials and we're all vying for the same patient population. But we're also vying for the site's resources.

Sponsors

Most sponsors (70 percent) said the hardest part of patient recruitment is finding the right investigators.

Big data and electronic health records are helping us get more savvy about identifying the right investigators. But more than 60 percent of investigators do only one or two clinical trials. With a constant churn of new investigators coming on board, additional training may be needed, and that adds to the timeline.

The FDA

The increase in patients required per drug application has soared 233 percent: from 1,500 in the 1970s to more than 5,000 today. This continues to put patient enrollment as the number one reason trials don't complete on time.

Given the challenges across the five groups, "one size does not fit all" is a truism. Each group has a unique role and set of challenges.

(Sources: www.clinicaltrials.gov, Tufts, ISR Reports data.)

Chapter 2:
Enrollment Timelines Drive Success

We sometimes hear "a third, a third, a third." A third of sites will meet and exceed their enrollment goals. Another third will probably just meet their enrollment goals. And a third of the sites will be unable to contribute to the overall enrollment goal.

There is definitely a correlation between how soon a site enrolls a patient into a trial to what their ultimate success is going to be in meeting their enrollment goals.

Enrollment timelines drive success in reaching enrollment goals:

Enroll within 30 days = 90+ percent chance of success

Enroll within 60 days = 50 percent chance of success

Enroll within 90+ days = less than 10 percent chance of success

It is critical to minimize as many delays as possible from study initiation to when the sites are actually able to enroll.

If a site can enroll a patient within 30 days from when the site is initiated, the site has a 90-plus percent chance of success.

If the enrollment gets pushed to 60 days, the site still has a fairly good chance. The site is at a 50 percent chance of success.

But if enrollment gets pushed to 90 days or later, the site has a less than 10 percent chance of success.

There are frequently issues that can cause delays at the very beginning of enrollment, such as the manufacturing of study drug compounds or the delivery of devices.

Incorporate this into your planning. If such delays happen, what are some of the communication efforts you can make with sites to make sure that they stay on board and will be ready to start when everything is in place?

What are the different milestones or key performance indicators that you could establish during your planning phase? Can you create a tiered plan to support the sites?

Sites are critical to success and they bear the highest level of responsibility in clinical trials. Sites develop relationships with patients to get them enrolled in the study and keep them engaged. They carefully conduct the study according to the protocol. Therefore, ongoing attention to proper and accurate site identification and feasibility is key.

Even the best sites will struggle with patient enrollment at some time during the recruitment period. This is why it is imperative to plan for the "what-ifs" of trials and be prepared to respond quickly to support the sites and their efforts.

Part 2: Planning Considerations

In this section we'll examine the criteria to consider in planning a recruitment or retention program.

Chapter 3:
Criteria to Consider

When you're planning a recruitment or retention program, there are many considerations. These eight are key:

Patient Population

Are the patients needed for the study available?

Disease Prevalence

What does the disease prevalence look like in the regions where you are conducting your trial?

Number of Patients

How many patients are required for your study?

Enrollment Timeline

What is the length of enrollment?

Location of Sites

How well does the location of sites match up to the geographic locations of your target population of enrollees?

Regulatory Agencies (Central IRB, Local IRB and/or EC)

Regulatory agencies, whether they are central IRBs, local IRBs, or even ethics committees, will be an additional element that you will need to include in your plan. This one criterion can have a significant impact on your timelines.

Communication With Sites

Do you have open communication with your sites? Is it a two-way communication or is it just you funneling information to them? When you need information back from the sites, how quickly and how readily are they able to provide it?

Metric Tracking

Any time you plan to roll out initiatives to support the sites, you want to make sure there is a way to track metrics.

Are your results not as successful as you planned? If so, what changes do you need to make?

Metric tracking helps you measure your return on investment and determine whether the initiatives you put in place were successful.

In Conclusion

Every study is different and needs a customized plan. Fully reviewing and evaluating each of these elements will help you determine where your energies will be best directed. In the next chapter, we will see how these elements were applied to different studies.

Part 3: Four Case Examples

In the following four case examples, you'll see how planning took on a different look and feel based on the therapeutic indication. The first three examples are focused on recruitment strategies and the last is focused on a retention strategy.

Chapter 4:
Case Example 1—Recruiting for a Pulmonary Disease Study

A highly prevalent chronic condition—chronic obstructive pulmonary disease (COPD)

Study Type

A phase 3, 52-week study investigating the effectiveness, safety and tolerability of medication on the exacerbation rate and pulmonary function in COPD patients

Study Details

Sites: 300 in North America
Patients: 1,500
Enrollment period: 12 months

Challenges Identified

From discussions with the sponsor, as well as by reviewing the study protocol, we immediately identified several challenges that could potentially impact the rate of enrollment:

Documentation

The study required that the COPD exacerbation (a flare-up where breathing function worsens) had occurred in a 12-month period prior to randomization, and it had to be documented and presented.

Pulmonary Function Test at Each Visit

Tests to measure lung performance can be unpleasant, and patients would naturally be resistant to taking part in these tests more than necessary.

Patient Travel to Study Sites

Mobility can be an issue with this patient demographic.

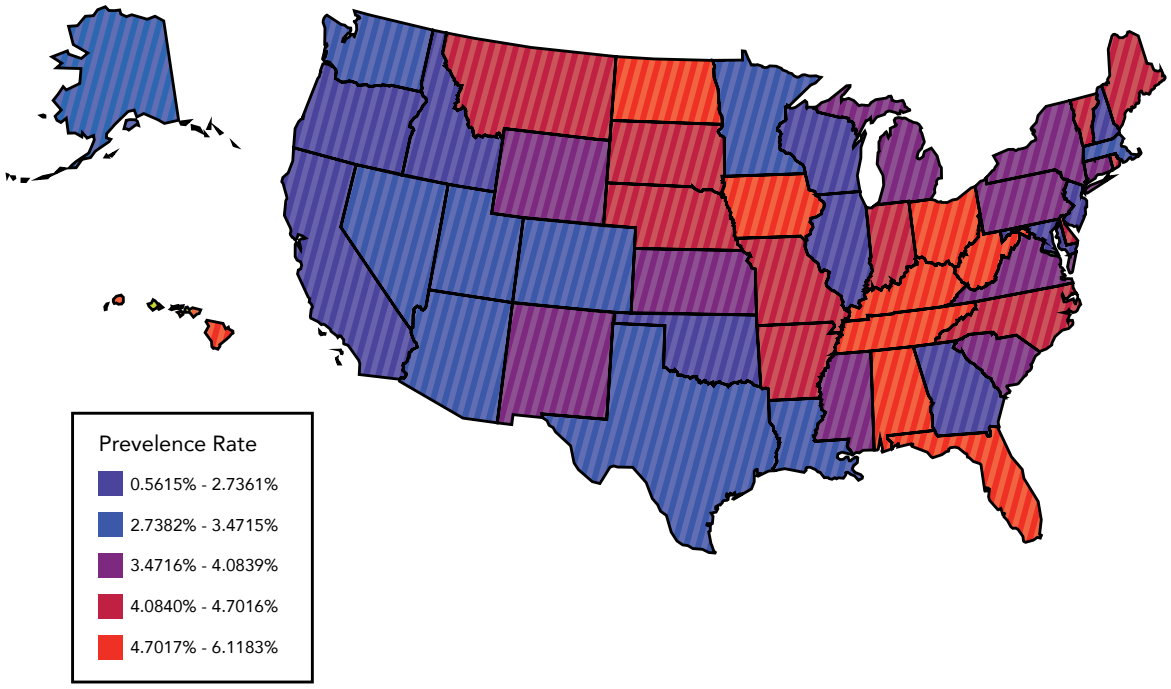
High Screen Fail Rate of 35 Percent and Higher

A high screen fail rate of 35 percent or higher was predicted. That required a plan with a wide net to keep the funnel full enough to process a sufficient number of individuals to be screened and then enrolled into the study.

Recruitment Considerations

Patient Population and Disease Prevalence

Using ICD-9 code claims data for North America, we created a prevalence heat map for claims associated with COPD:



The blue areas are cold, meaning lower prevalence, and the red areas are hot, meaning higher prevalence.

In this case, we see that the prevalence is higher in the Midwest and eastern states.

Number of Patients and Sites

When you overlay the protocol requirements and the disease prevalence, it becomes more finite. The study would need to screen 3,750 patients to yield 1,500 enrolled.

More and more, we are finding a need to support the sites with external enrollment efforts. This is not meant to criticize sites—it's just that competition is growing and additional support elements are required.

Regulatory Agencies and Timelines

The majority of these sites were central IRB, which allowed us to get materials approved and rolled out quickly, within 45 days of contract execution.

This is something to take into consideration in planning programs. If you have a study, for example, a late-stage oncology trial, you may be working with a lot of academic centers that have local IRBs that might meet less frequently than central IRBs, perhaps only once every one or two months.

Communication

Direct communication with the clinical research coordinators improved metric tracking and reporting.

Do you have strong communication with the site coordinators and investigators? That's really important for two reasons.

First, it keeps the sites engaged and motivated to pay attention and focus on your trial. And it's extremely helpful when you need to get information and metrics back from those sites to determine whether the program you've put into place is successful.

Recruitment Initiatives Executed

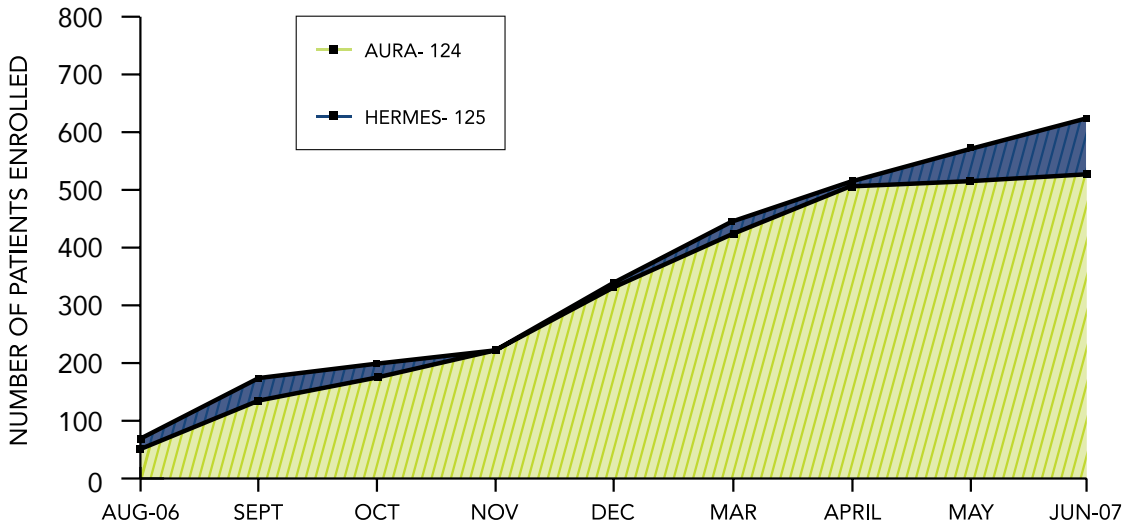
A multitude of complementary strategies were required to ensure successful study completion, including:

- Study branding
- Study awareness materials for the sites
- Recruitment kits (study-specific educational materials)
- Community outreach

- Physician outreach
- Targeted advertising
- Study website
- Direct mail
- Retention support (transportation assistance, stipend management, etc.)

There was a 12-month enrollment program and an 18-month study participation period. There were concerns that over time, individuals would start to be lost to follow-up or not maintain study compliance because they were unable to come to all study visits without some additional support. The retention support initiatives made a difference.

Enrollment Outcomes

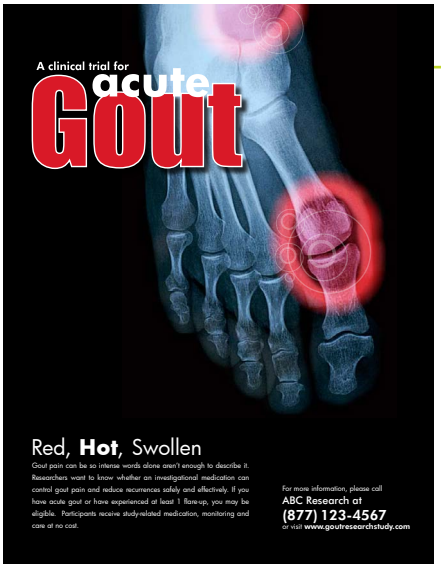


In this study, there were two identical protocols running simultaneously and we supported them together.

The enrollment goals were met on time. The plan produced positive results. It helped the study stay on track with where they needed to be and ensured that they would meet their enrollment goal.

This was not a rescue case study—it was all proactively planned. All of these considerations were worked out at the forefront of designing the recruitment program.

Chapter 5:
Case Example 2—Recruiting for a Gout Study



An acute condition—gout

Study Type

A phase 2 study evaluating the safety and efficacy of medication in the treatment of acute flares in gout patients who are refractory or contraindicated to NSAIDs and/or colchicine

Study Details

Sites: 35 in the U.S.

Patients: 50

Enrollment period: 6 months

Challenges Identified

5-Day Patient Identification Window

Gout is a fairly prevalent disease in the U.S., but the 5-day patient identification window made our patient population more difficult to recruit.

Recruitment Considerations

Criteria to Consider

Number of Patients and Sites

The minimum site enrollment requirement was 1.5 patients per site.

Regulatory Agencies and Timelines

A majority of the sites were central IRB, allowing us to get materials approved more quickly.

Communication

Direct communication with clinical site coordinators assisted in the flow of information.

Recruitment Initiatives Executed

Due to the challenges identified at the onset of the program, recruitment solutions were twofold:

The Treating Physicians

Focused on identifying and accessing patients at the point of care.

We walked through the study process with the physicians and came up with the identification and referral process with them, and if there were gaps, we worked together to close those gaps.

Direct to Patients

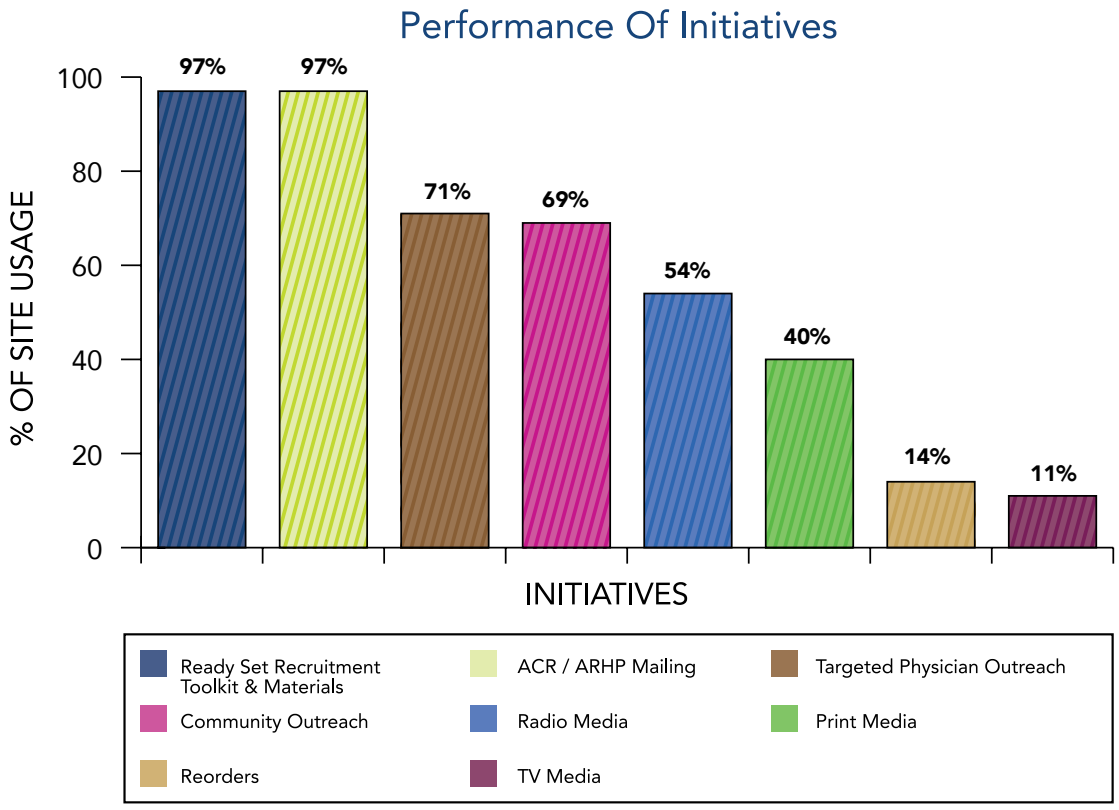
Outreach to targeted gout patients with regular flare-ups.

We reached out directly to patients who had regular flare-ups. We did this through support group organizations within the communities where the research sites were located, as well as through a targeted advertising support program.

The recruitment campaign was adopted by most of the sites. Often the sponsor will give sites the option.

Strategies Included:

- Educational study materials
- Patient identification tools
- Community outreach services
- Targeted advertising support
- A targeted physician referral program



Campaign Performance

Overall, the recruitment campaign was adopted by 60 percent of sites. The highest adoption rates were seen with direct physician mailing and the use of recruitment toolkits. We found that radio advertising drove the highest amount of external referrals to the sites.

The study finished two months early.

Chapter 6:
Case Example 3—Recruiting for a Raynaud's Study

A Rare Disorder: Raynaud's Phenomenon

Study Type

A phase 2 study to assess efficacy of a once-daily administration of a medication for the treatment of vasospasm in primary and secondary Raynaud's phenomenon

Study Details

Sites: 71 in 14 countries

Argentina	Korea
Canada	Mexico
Colombia	Poland
Czech Republic	Spain
France	Sweden
Germany	United Kingdom
Hungary	United States

Patients: 208

Enrollment period: 10 months

Recruitment Considerations

Challenges Identified

Small Patient Population

It's estimated that about 3-5 percent of people worldwide have this condition.

Recruitment for Primary Raynaud's More of a Challenge Than Secondary Raynaud's

About 10 percent of primary Raynaud's patients have secondary Raynaud's, which means the disease is secondary to other conditions.

Patients Must Have Fairly Active Disease

Another criterion that further narrows the size of the patient population.

Potential Patient Concerns Related to Concomitant Drug Restrictions and Washout Periods

It's natural for patients to want consistent treatment.

Study Design and the Possibility of Receiving a Placebo

It's common for patients to be resistant to joining a study when faced with the possibility of being assigned to a placebo group.

Exclusion of Smokers

This restriction could be an issue internationally, since some countries have a higher percentage of smoking populations than the U.S.

Criteria to Consider

Patient Population and Disease Prevalence

Limited patient population due to limited disease prevalence, coupled with study criteria.

Number of Patients and Sites

The breakdown between primary and secondary Raynaud's is definitely a strong consideration when determining strategies.

Tracking Outcomes

Results should be trackable so you will be able to evaluate the individual performance of each initiative.

In rare/orphan indications, you want to evaluate and consider what it means for an individual to participate in a trial. Oftentimes, strategies that we would consider retention-oriented can also indirectly play a role as part of a recruitment strategy. If we can offer a solution during the recruitment phase that provides support down the road

to the patient, it may be just the reassurance they need when making the decision to participate in the trial.

Recruitment Initiatives Executed

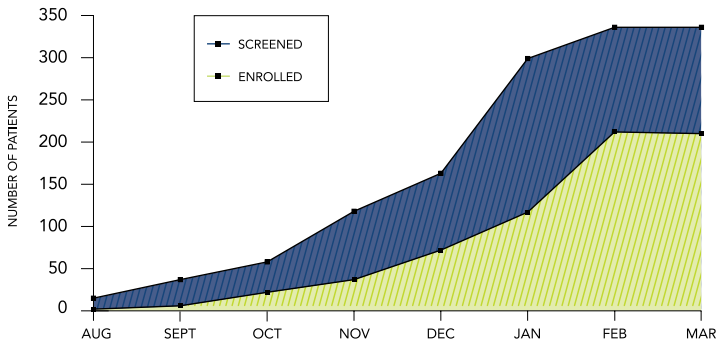
With all considerations taken into account, a multilayered approach was needed to target the desired population. This was accomplished through the following:

- Aggressively engaged study sites to build a strong relationship with the study staff
- Raised internal study knowledge to keep sites focused on identifying patients
- Expanded study awareness among the targeted population and their families to drive patients to self-refer
- Educated Raynaud's patients so they could make an informed decision about study participation
- Built physician relationships to ensure a strong patient referral network

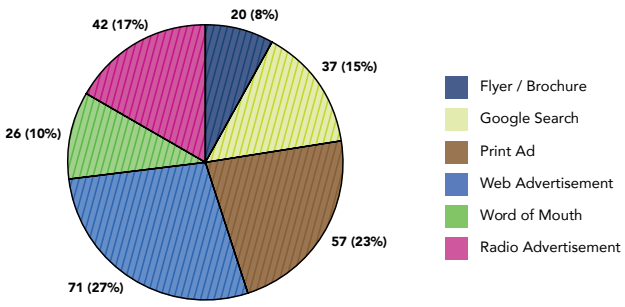
Campaign Performance

The study enrolled three months early and achieved 213 patients out of the 208 target.

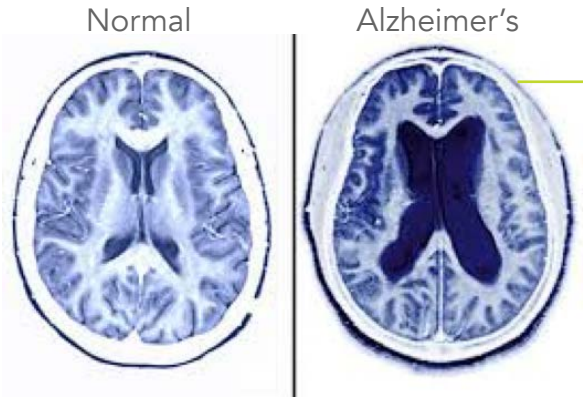
Enrollment Progression



Number Of Referrals By Source



Chapter 7:
Case Example 4—Retaining Patients in an Alzheimer's Study



An older patient population—Alzheimer's disease

Study Type

A phase 3 study to evaluate the safety and efficacy of a medication in subjects with mild to moderate Alzheimer's disease

Study Details

Sites: 176 in the U.S.
Patients: 2,285
Retention period: 22 months

Retention Challenges Identified

The Nature of the Disease

Alzheimer's disease limits the patients' capabilities and creates a need for study compliance support.

Caregiver Considerations

The study would create an additional commitment and logistical challenges for the caregiver.

Potential of Adding to Ongoing Stress

Caregivers of Alzheimer's disease patients deal with stress on a daily basis and this compounds over time.

Mild Adverse Events Experienced by Patients

Headache, dizziness and fatigue were the top three adverse events noted by patients who had discontinued participation.

Length of Study Visits

With 60 minutes required for the infusions, additional assessment time, and downtime between the exam, testing, meeting with the investigator, etc. meant a significant commitment for each visit.

Frequency of Study Visits

Visits every six weeks can be challenging for caregivers.

Current Rate of Attrition

There were two identical protocols running simultaneously and we supported them together. Attrition rates in study A and study B were respectively 8 percent and 9 percent.

Number of Patients Needed

A minimum of 920 patients and 650 patients were required to maintain statistical power in study A and study B respectively.

Retention Considerations

Criteria to Consider

Patient Population and Disease Prevalence

This was an older patient population with limited mobility and dependence on a caregiver. The caregiver's responsibility and involvement in the study was also a factor for success.

Number of Patients and Sites

The goal was to retain patients, so our focus was on the known reasons why patients were electing to discontinue the study.

Regulatory Agencies and Timelines

Since our involvement began after the study was already underway, it was important to consider what would be required to obtain regulatory approval for our new initiatives, such as an informed consent form addendum to provide stipends to patients electronically. Changes would obviously impact timelines.

Communication and Tracking

Open communication was required with the sites, clinical research associates and the sponsor to identify and fully understand retention issues and concerns.

Retention Initiatives Executed

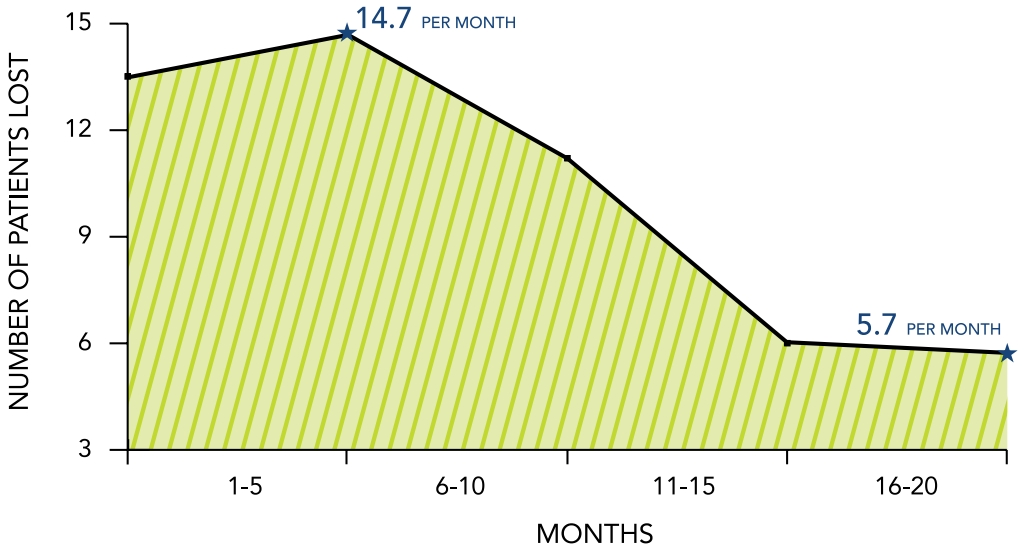
Objectives for the program were twofold: Reduce monthly attrition rates, and engage patients and caregivers regularly throughout the study.

It was also important to maintain site engagement and enthusiasm throughout the study.

The Strategies Used Supported the Patients, Caregivers and Sites:

- Study visit activity kit
- Patient and caregiver support items
- Educational and motivational materials and messages
- Web portal for patients/caregivers and sites
- Transportation assistance
- Electronic stipend payments
- Continuing education unit articles for staff

Campaign Performance



Within 30 days of program rollout, attrition began decreasing by as much as 25 percent. Overall, attrition decreased by 61 percent and remained constant.

The success of this program resulted from two main things:

- Site buy-in to the program and openness to use the services provided
- Constant and encouraging communication with the patient and caregiver throughout the remainder of the program

Our goal was to make participating in the study as convenient as possible for the patients and caregivers and to make them feel important for their contribution to the study.

Afterword

In this ebook I've tried to cut through some of the complexities of clinical trial recruitment and retention by presenting planning considerations and showing real-world results. I hope you've found some pearls of wisdom here that will help, and I wish you the best as you plan your own enrollment programs.

About the Author

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Melynda is a 22-year DAC veteran with expertise that spans protocol planning, recruitment, retention, global regulations, emerging markets and more. She was instrumental in DAC's rise from a niche site management organization to a global recruitment and retention leader. Melynda is a 2008 inductee into PharmaVoice magazine's 100 Most Inspiring People in the Life Sciences. She has written extensively for clinical trial trade publications, blogs at ImperialCRS.com and is co-author of the ebook Your Patients Are Here: Where to Recruit & How to Retain Highly Engaged Patients.

Next Steps

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