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Challenging the 'Site-first' Status Quo in Patient Enrollment

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Case study highlights a new patient-centric enrollment model that uses a data-driven approach to identify qualified patients first.

PATIENT CENTRICITY

The great operational challenge of clinical trials is to identify and enroll qualified subjects. This essential first step continues to be the point at which most studies stumble and may even fail. Historically, sponsors have relied on study sites to recruit and enroll patients, depending on sites to estimate the number of qualified patients they can access, and focusing on the selection of patient-rich sites to achieve enrollment targets.

Years of industry benchmarking have documented the limitations of this "site-first" practice, which typically leads to enrollment delays and follow-on increases in research time and cost.[1,2] Despite the efforts of sponsors and contract research organizations (CROs) to improve the selection of optimal investigative sites, all too often the result is low enrollment across a large number of sites, with most of them enrolling too few subjects.

Slow and insufficient recruitment leads to prolonged study enrollment, followed by the conventional "fix" of adding more sites and, often, adding sites in more countries. This further dilutes enrollment rates, driving up costs and delaying time to product approval. The fact remains that a site rich with a population of *potential* patients does not necessarily translate to *actual* enrollment of randomized study subjects.

In recent years, some improvements have been gained by leveraging electronic medical record (EMR) data to identify potential study participants. Although EMRs can alert caregivers to a potential subject within a medical dataset, that information must be referred to study investigators to translate into randomizations. Treating physicians, who are increasingly overwhelmed by "alert fatigue," lack time and motivation to act on growing numbers of EMR alerts to patient matches for a prospective study.[3]

Persistent failure to achieve enrollment on time and within budget is due in large measure to continued reliance on investigational sites for feasibility assessment and patient recruitment—practices that demand expertise and capabilities beyond their scope.

Sites routinely overestimate the numbers of patients they will be able to enroll, generating false positives that result in under-enrollment, the need for additional sites, and cost over-runs. The use of EMR and de-identified patient health claims data improves the identification and location of potential patients with a target disease indication. But only a subset of these populations actually will qualify for or be interested in participating in a specific study.

Increasingly complex study protocols make it more difficult to identify qualified subjects within a population of accessible patients, and there is more competition than ever for those patients who do qualify. For recruitment, sites still rely primarily on traditional methods—physician referrals, complemented by print, radio, and television ads—approaches that are increasingly inadequate in the crowded research landscape.

A better way: Put patients first

Sophisticated data mining, analytics, and social media are creating new platforms to conduct highly effective feasibility assessment and patient enrollment. To overcome the limitations of the site-first approach, PPD

developed a patient-centric methodology that randomizes more patients to fewer sites in less time by identifying qualified patients before selecting sites. The patient-first model depends upon the integration of PPD clinical trial services with those of Acurian, its enrollment affiliate, and the dedicated site network, Synexus.

This model was developed in the context of enrollment challenges facing clinical research in chronic ambulatory disease indications. Populations of potential study patients are abundant in asthma, diabetes, hypertension, atopic dermatitis, hyperlipidemia, osteoarthritis, and other prevalent, non-acute diseases. The difficulty is in identifying qualified and interested patients, and channeling them to selected investigational sites.

Strategic enrollment: Finding qualified subjects in a pre-screened population

Central to this model is the use of proprietary databases that enlist patients who express interest in research participation and who provide self-reported health and household information. Both the strategic enrollment consultant and the dedicated site network maintain and expand proprietary databases.

Database population. Proprietary databases used in PPD's model have amassed information on pre-screened patients across thousands of studies, retaining information for all patients screened, as well as for the smaller percentage of patients randomized to studies. Acurian's database currently holds information for 20 million pre-screened individuals and 100 million identified households across 70 countries. An estimated 10,000 people are added daily as strategic, multichannel advertising campaigns recruit great numbers of potential subjects for new studies.

Subject identification and modeling. Study-specific data mining and profiling begin with the identification of database members with the relevant disease indication. Patient-provided health information drives more targeted identification of subpopulations most likely to meet a given study's inclusion/exclusion criteria. Potential subjects are invited to contact recruiters through multiple channels—online, call-in centers, pre-screening visits—to learn if they quality.

To better understand this population of pre-qualified patients and increase confidence in randomization, interviews, surveys, and historic study data are leveraged to determine their interests and motivations in study participation and to identify potential barriers to enrollment. Targeted patient modeling takes into consideration criteria from clinical data and demographics to lifestyle attributes, online activity, and household purchasing patterns.

Feasibility and mapping. Based on the pool of pre-qualified patients, highly predictive, proven enrollment models are used to define the number of patients that can be enrolled for given study. Patient locations are mapped geographically to identify patient-rich areas most suitable for study sites. Geographical mapping also informs the best approaches for targeted advertising and the best communication channels to use in recruitment, which can vary dramatically by location.

Recruitment and engagement. In the patient-first model, recruitment goes hand in hand with patient engagement and education to communicate a clear understanding of study benefits and the commitment required of subjects. Pre-screened and pre-qualified subjects receive ongoing information on the purpose, value, and process of studies to build an informed and committed patient cohort, while improving retention.

Pre-qualified subjects are followed throughout the enrollment process, sharing their disease and treatment experiences and contributing their views and preferences related to study procedures. All of this patient intelligence is fed back into the database to inform subject identification for future studies.

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Social media also is used to connect patients directly to researchers and leverages self-reported patient data to locate and enroll patients who meet a subset of inclusion/exclusion criteria for a specific trial. After modeling and mapping locations, potentially qualified patients are channeled to high-performing study sites—network and non-network—matched to their locations.

Referral. Patient identification operations are closely integrated with enrollment conducted at the sites. Pre-qualified candidates are referred to appropriate sites using intelligent matching algorithms that can help improve program efficiencies by applying nested protocol logic and site staffing capacity.

Site selection: Benefits of a dedicated site network

Based on the qualified patient population identified from the databases, PPD defines the location and number of investigative sites required to meet enrollment targets. The model draws first from the nearly 200 dedicated and affiliated sites in the Synexus network, and then from additional top-performing traditional sites as needed. The global network of dedicated sites boosts efficiencies using shared processes and streamlined operations to ensure that regulatory submissions and other startup activities are completed by the time the first patients are referred. These Synexus sites pre-screen patients in anticipation of site activation, allowing for screening to commence immediately thereafter.

Recruitment and enrollment support. Synexus has a comprehensive range of recruitment methods to support study enrollment across the network of sites. Recruitment strategies and tactics are

monitored and adjusted throughout a study lifecycle to optimize the match of patient to site.

Face-to-face engagement. Site engagement strategy puts patients at the center of trial preparation and management. Each strategy is tailored to the specific circumstances of the patient community. All Synexus sites engage with primary care providers, specialists, and pharmacists to establish a network of healthcare professionals and integrate with the local health system to support study-specific requirements. Network sites conduct patient interest visits—non-study-specific encounters that introduce patients to the site and provide an opportunity for them to meet with a member of the medical team. Patients hear about the research process and the role of a study participant. These visits enable patients to make more informed, committed decisions about clinical research participation.

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Global standards. Conducting all trial activities at dedicated research sites offers additional support for the patient-centric model. Patients can be managed throughout the lifetime of the study. Global standards, procedures, and training are in place at all sites, contributing both to high quality and to significant cost and time reductions across studies and entire development programs.

Global cholesterol study: Patient-first model reduces startup time

PPD's approach was used to accelerate enrollment in a global Phase III program to evaluate a lipid-lowering therapy. The program included three studies to be conducted in 13 countries across the U.S., Europe, and Africa. Target enrollment was 3,400 patients, and the sponsor needed to meet aggressive timelines: the goal was to screen the first subject no later than 3.5 months (107 days) after delivery of final protocol for the first study.

Synexus provided 83 of the 277 sites used in the three Phase III trials. Based on the patient-first identification methodology, PPD screened 5,299 patients in 114 days and enrolled 3,660 subjects in 126 days. Compared to industry benchmarks based on 2014 to 2016 trial performance data, the patient-first strategy reduced startup across the three studies and all 13 countries by 47%. The slowest-enrolling country (Sweden in study 1) reduced startup time by 24%, while the fastest-enrolling sites, in the U.S.-based study 2, reduced startup time by 88%.

In the first 30 days of the program, 39 investigative sites were activated, 390 patients were screened, and 115 patients were enrolled. Other acceleration measures, compared to industry benchmarks, include:

- First protocol received to first site active: 63% faster
- First site activated to last site activated (over three studies): 73% faster
- First subject randomized to last subject randomized (over three studies): 72% faster
- First protocol received to last subject randomized (over three studies): 62% faster

Aligning operations with patient needs

The value of patient centricity is increasingly recognized in drug development, but the term "patient-centric" is often more buzzword than methodology. A working definition, co-developed by patients, caregivers, and community advocates, characterizes patient centricity as: "Putting the patient first in an open and sustained engagement for the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family."[4]

PPD's enrollment model operationalizes this principle, leveraging in-depth patient information and insights to speed enrollment, minimize the number of study sites, and accelerate startup. The ultimate goal of patient centricity is to develop therapies more closely aligned with patient needs. The patient-first recruitment model demonstrates that patient-centric approaches also can address the needs of sponsors to reduce research time and cost.

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