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WHITEPAPER

What every clinical team should consider before developing the next protocol: Putting volunteers first

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patheon

Abstract

Momentum continues to build around “patient centricity,” a concept that is captivating the biopharmaceutical industry and spawning everything from articles and conferences to surveys, webinars and lively LinkedIn exchanges. And while everyone applauds the renewed focus on patients as a positive development, some say it is time for biopharma companies to turn their attention to another audience without whom drug development would be impossible—clinical trial participants. For one thing, there is an important distinction between the two audiences, according to representatives of investigator sites, who operate on the front lines of clinical research. “Although individuals who participate in clinical trials are often referred to as patients, they really aren’t patients – they’re actually volunteers,” said Therese Dayton, RN, CCRC, Director of Nursing and Operations at Rochester Clinical Research (RCR) in Rochester, NY. “They volunteer their time and medical treatment during a trial which is not guaranteed,” she added, explaining, “Volunteers could receive a placebo or an unproven or ineffective treatment. That’s the whole point of research.” As a result, investigator sites eschew the phrase “patient centricity” in favor of “volunteer centricity”.

Only about 5% of those eligible to participate in trials actually do so, even though the number and size of studies have been escalating. Those who do volunteer to participate in trials can face some frustrating experiences, thanks to what could be characterized as a combination of faulty communication and protocol missteps. Among them: hard-to-open drug packaging, unclear directions about following complex regimens, an escalating number of required medical procedures, malfunctioning technology, and clinic appointments that must be cancelled—again—when supplies fail to arrive.

The issues may be a consequence of a failure to consider the needs of volunteers during the protocol development process. Beyond engendering frustration among volunteers and the site staff who interact with them, such issues potentially endanger drug development by eroding the three cornerstones of clinical research—adherence, retention and recruitment. At a time when companies are readily embracing new opportunities to engage patients, they would do well to dismantle barriers to clinical trial participation by making subjects the centerpiece of the protocol planning process. “Volunteer-centric” trials engage subjects as partners in clinical research by making participation easy, positive and comfortable experiences for them. Doing so has the potential to launch a new era of volunteer-centric clinical trials that, aside from being efficient and cost-effective, establish a cadre of research ambassadors—volunteers whose experiences are so fulfilling that they join additional studies and encourage friends and family to do the same.

Read this whitepaper to learn why even though everyone applauds the renewed focus on patients as a positive development, some say it is time for biopharma companies to turn their attention to another audience without whom drug development would be impossible—clinical trial participants.

Patients or volunteers?

However popular and well-intended the phrase may be, in the clinical research arena "patient centricity" is considered a misnomer. "Volunteer centricity"—defined as making trial participants the focus of protocol planning—is preferred. "Patient" has never been considered the proper terminology for study participants.

For one thing, individuals who participate in clinical trials are volunteers, not patients, which is an important distinction. The word "patient" implies going to a doctor's office for care, but there is no implicit guarantee of medical treatment when someone participates in a clinical trial.

"Volunteer centricity"—defined as making trial participants the focus of protocol planning—is preferred.

A volunteer could be randomized to a placebo or to an untested or ineffective treatment; some study participants are merely observed. Another reason is the volunteer nature of a clinical trial.

Participants volunteer their time and can withdraw their gift of time whenever they wish. "Volunteer centricity"—defined as making trial participants the focus of protocol planning—is preferred.

"Volunteer" emerged by default as a term preferred by some leading investigator sites, which subsequently coined the phrase "volunteer centricity" to emphasize the importance of making clinical trial volunteers the centerpiece of study planning and processes. "Volunteer" is often used interchangeably with "subject." Historically, the industry has referred to individuals who participate in clinical trials as "subjects." Although "subject" is commonly used, some perceive it as disrespectful or even pejorative.

Regardless of whether they are called volunteers or subjects, the point is that effective protocol planning considers the impact of the protocol on the individuals—both volunteers and investigator site staff—who will carry out the study.[1, 2, 3, 4]

An evolving clinical research environment

More often than not, sponsors develop protocols with a focus on testing clinical endpoints and somewhat less attention on the practical implications of the design on subjects and investigator sites.

One reason is that clinical teams rarely consult investigator sites about how efficiently a protocol can be implemented in the clinic or whether a sufficient number of volunteers are available to participate.

The lack of input can leave both sites and subjects unprepared for what lies ahead. Sites face the challenges of time, space, recruitment and logistics that protocols demand, and subjects face the demands of ever-more-complex protocols.

In the past 15 years, there has been a dramatic increase in protocol complexity as sponsors sought to collect increasingly larger amounts of clinical research data. In a typical Phase III protocol, for example, the total number of endpoints grew 47% (to 13 from 7) and the total number of procedures grew 37 percent (to 167 from 106) between 2002 and 2012, according to the Tufts Center for the Study of Drug Development (CSDD).

Examples include invasive procedures, x-rays and imaging, heart activity assessments, lab tests and blood work, routine examinations, and questionnaires and subjective assessments.

Many of the procedures are considered "non-core," meaning that they are unrelated to the endpoints of the trial. Non-core procedures increased by 31 percent during the same period. This illustration shows the growth in procedures in Phases I - IV during the 10-year period from 2002 through 2012. (Figure 1)

One reason for the hyper-complexity of protocols is the shifting focus of investigational drugs to tougher targets. These include chronic diseases in the areas of oncology, immunology and central nervous system (CNS).

Another is intensifying competition between biopharmaceutical companies, which compels sponsors to gather more data as a means of differentiating their products in crowded markets. Unfortunately, complex protocol designs are associated with high study volunteer dropout rates, further burdening investigator sites that are already stretched thin.

According to a 2011 Tufts CSDD survey of nearly 16,000 global sites, 37 percent under-enrolled some studies, while 11 percent failed to enroll a single volunteer for other trials. Two years later, another Tufts CSDD study revealed that nine out of 10 clinical trials worldwide fail to meet their patient enrollment goals.

Site representatives acknowledge that the loss of evena single volunteer is "painful" at a time when more protocols are requiring hard-to-recruit volunteer populations or volunteers from small pools of individuals for the increasing volume of orphan drug studies.[4, 5, 6]

As studies continue to increase in size, number, length and complexity, the ability to recruit and retain sufficient volunteers—already a difficult prospect, say investigator sites—will be tested further.

Growth in procedures in Phases I-IV from 2002-2012

	Phase I	Phase II	Phase III	Phase IV
2012 unique procedures (median)	30.3	29.2	28.4	26.4
10-year growth	35.3%	58.8%	43.0%	46.3%
2012 total procedures (median)	191.6	192.1	146.6	96.1
10-year growth	32.4%	64.1%	56.6%	62.6%
2012 total work burden (median)	50.9	56.6	42.0	28.1
10-year growth	48.4%	73.1%	55.6%	56.9%

Figure 1

Role of clinical sites: The human factor

Regardless of the changes underway in the world at large, the human factor is likely to remain a crucial element in the clinical trial arena. Research indicates that study volunteers want a one-on-one relationship with someone they trust who can alleviate their fears and apprehensions, help them understand how to follow a regimen correctly and look after their interests.

Volunteers find those relationships among investigator site staff, something the sites readily acknowledge. "The relationship between the volunteer and site staff is key," acknowledged the head of one clinical site.

While volunteers may not be able to identify the sponsor of a blinded study, they know the site and the staff members with whom they interact. The sites—regardless of whether they are stand-alone research facilities or local medical practices, hospitals or clinics—are part of the local community.

Meanwhile, the individuals who staff them function as the human faces of trials. Site staff are responsible for recruiting and enrolling subjects, instructing them on how to follow the protocol, monitoring their progress and doing everything possible to retain them through the conclusion of the trial.

Site staffs interact with volunteers on a day-to-day basis, so they often get to know them well. Sites maintain databases of potential volunteers, who often participate in multiple studies over time. As such, relationships between volunteers and site staff may span months or even years. As RCR's Therese Dayton puts it, "Some participants become like family to us."

Aligning clinical supplies to end users

Because investigator sites work closely with volunteers, the issues that affect subjects inevitably impact the sites, as this case study illustrates. While some, like those in the flu study, involve procedures, many issues are those of clinical supplies and equipment.

Supplies and equipment are at the heart of clinical trial experience for both the volunteer and the site. At best, these issues can be irritating and inconvenient, but manageable. At worst, they have the potential to derail a protocol through errors or as a consequence of poor adherence or retention. Failure to retain volunteers in an ongoing trial is considered "the worst thing that can happen" from a site perspective.

Here are some examples of common supply and equipment problems that impact the lives of volunteers and sites.

What would your grandmother say?

All too often, sites say product packaging is not designed with end users in mind. One example: The use of childproof packaging in a trial of an arthritis drug. Another is the wide use of blister packaging, which can be difficult to open even for average volunteers. If blister cards will be used, sites say clinical teams should consider providing a tool to help subjects open them. The size of drug packages can be a problem as well; some blister packs can be as large as placemats. This makes it difficult for a subject to carry drug discreetly in a handbag or briefcase, for example.

The bottom line: Consider the subject who has to access the drug in a real-world environment. If it is difficult to access or carry the drug, adherence is likely to suffer.

CASE STUDIES

A tale of two trials

Such relationships can play a key role in retention, something that two recent influenza studies illustrate. The endpoint for both studies – one of them completed, the othe ongoing – is the appearance of flu symptoms.

Trial 1

Subjects were 200 adults over age 65, who were followed closely for two years, or two entire flu seasons.

In this trial, volunteers were contacted in two ways. The same "friendly, live person" on the investigator site staff phoned the subjects every two weeks to ask if they were experiencing any possible cold or flu symptoms.

In addition, an individual from a call center phoned the volunteers twice weekly to ask them a set script of questions. If a volunteer reported possible cold or flu symptoms to either the site staffer or the individual from the call center, arrangements were made for the volunteer to come to the clinic for a culture.

The trial ended after two years with a retention rate of 100 percent. "We did not lose a single person," a site representative of the site reported proudly. "That's volunteer centricity."

Trial 2

In the second trial, 300 adults—100 aged 50 to 65 and 200 aged +65—are being followed for one year, or one flu season. This trial is ongoing and will end after the current flu season.

Here, the investigator site calls the volunteers every two weeks to inquire about whether whether they are experiencing possible cold or flu systems. In addition, subjects are required to call an automated system twice weekly to answer a series of six questions. Volunteers must respond to the questions by pressing the key pad a minimum of six times, followed by the hashtag.

A 'yes' answer to any of the questions prompts follow-up questions. As with Trial 1, if a volunteer reports possible cold or flu symptoms, an appointment is made for the volunteer to visit the clinic for a culture.

Unfortunately, the automated system has been a continuing source of problems. It features a heavily accented British voice that confuses many of the elderly volunteers by mispronouncing familiar terms and using others with which they are unfamiliar. "The subjects are primarily over age 65 and many don't know what a hashtag is," one site staffer observes.

The automated system is frequently overloaded and when this happens, it fails to register the volunteers' calls. As a result, every Monday the investigator site receives a list of as many as 60 subjects who were identified as noncompliant. When site staffers contact these volunteers, many are frustrated and upset. They insist they did call, but the automated sstem cut them off or hung up.

Over time, a number of subjects have dropped out of the study, citing frustration with the system and annoyance with the volume of calls they have to make. Many also expressed the feeling that their honesty was being questioned when they were contacted for being noncompliant after having called the automated system as directed. Staff at the investigator site say they are expecting the study to be "a relative disaster," with a retention rate of 80 percent at best. They speculate that the study will be repeated.

After years of experience with countless trials and volunteers of every age, the staff says it would be worthwhile for clinical teams to think through what they are asking of subjects in a trial and consider whether these expectations are reasonable.

They further say the flu studies support the importance of human interaction in the clinical trial arena. Volunteers of every age express a strong preference for interacting with a person instead of an automated system.

Make labels readable

Labels in 4-point type, Excel spreadsheets with columns of random 12-digit numbers to match with drug supplies, and a plastic bag containing 100 tiny vials bearing miniscule labels – site staffers can rattle off example after example of what they call "impossible-to-read" product labels. Sites say this is more than a matter of inconvenience for them. "It takes two people reviewing them with a magnifying glass, which puts us in danger of dispensing the wrong drug," one related.

The bottom line: Use bigger fonts and different colors to make labels easy to read. If an average person is unable to read the label without assistance, the font is too small and errors are possible.

Clarify complexity

As protocols become more complex, so do dosing regimens. Complex dosing regimens put additional pressure on sites and volunteers – sites because they have to instruct volunteers about how to take the drugs, and volunteers because they must follow instructions to the letter. The elderly in particular can have difficulty with complex regimens that may require them to take one tablet from one bottle in the morning, for instance, and two tablets from another bottle at night. Conveying directions in a clear and easy-to-follow way can prevent errors from affecting adherence.

The bottom line: Make complex regimens easier to follow by using visual aids, such as screen shots, that demonstrate in a step-by-step way how to take the regimen.

Use thought in blinding

While blinding is a critical element in clinical research, sites say it is just as important for them to be able to easily distinguish between blinded drugs in order to conduct a trial. Consider an adjuvant vaccine study in which contents of two vials had to be mixed in different ratios, but the vials were tiny, identical, in the same kit and bore virtually identical labels of the same size and color. "Our biggest fear is making a mistake," one site representative said. "Why not a different color label or cap on one vial?" Pre-filled syringes are another alternative.

The bottom line: Help site staff differentiate between blinded drugs to prevent errors in any way possible—with colored print, labels, vials or caps—or by eliminating the need to combine the contents of different vials through the use of pre-filled syringes.

Choose the right technology

The right technology is a boon to clinical trials, but faulty technology or technology that is not well matched to the abilities of study subjects defeats the purpose. In one recent trial, the sponsor provided a bar code scanner that was expected to reduce site workload; unfortunately, as it turned out, the scanner could not read the bar codes on the study drug. In another, subjects received an iPhone, but problems quickly ensued. "It was a trial involving 75-year-olds," explained a member of the site staff. "The ability of 75-year-olds to use an iPhone is not the same as younger volunteers, but we didn't have any input into the decision."

The bottom line: In choosing technology, consider consulting investigator sites for their views. Always ask this question: Will the volunteers in the study be capable of using this technology with ease? Also, test technology before it reaches sites and subjects in order to uncover and address any performance glitches.

Say what and when

Sites often do not know what materials and equipment are being provided for a study and when to expect them to arrive. "Exactly when we'll get supplies is always left out of the chain of communication," said a site staffer.

With ever-tightening study timelines becoming the new normal, investigator sites say studies could get underway promptly and their lives would be far easier if they weren't kept in the dark.

"Imagine a morning when we're busy seeing fasting patients and UPS arrives, bringing us these huge boxes, some of which are temperature-sensitive and marked 'must open immediately,'" one site representative related. "Now we have to drop everything to address the boxes that have just arrived."

Inconvenience aside, supply missteps can sabotage recruiting efforts. One site enrolled 40 volunteers for a study, then received supplies sufficient for only eight. In another example, appointments with 55 subjects had to be rescheduled one week when an expected supply of vaccine did not arrive, prompting some volunteers to drop out of the trial.

In cases such as these, "the sponsor is unaffected because the subject doesn't know who's conducting the trial, but our reputation is on the line because the subjects think we're idiots," a site representative said ruefully.

The bottom line: Communicate. "Amazon and Zappos can tell customers when their packages will arrive, and we need to know, too."

Avoid mysteries

The process of supplying a clinical trial is complex and often involves multiple sources—a sponsor manufacturing a drug, a third-party supplier packaging and distributing that drug, a clinical research organization (CRO), ancillary providers and so on. Although sites often conduct multiple studies, many suppliers fail to designate the protocol on shipments of supplies and equipment in order to protect the blind.

This leaves sites scratching their heads when unidentified packages arrive. Some sites sequester such materials in a "mystery room of surprise packages" until they can identify the study to which they belong.

One site representative related a story about the arrival of a life-sized female mannequin shortly before Halloween. The package bore neither a protocol number nor an explanation, so everyone was mystified.

A staff member known to be a "Halloween fanatic" made plans to dress up the mannequin and make it the centerpiece of the site's holiday party until the day a matching male mannequin arrived. As it turned out, the mannequins were provided by a sponsor so site staff could teach subjects how to self-inject for a clinical trial that was about to start. "The protocol didn't even mention a mannequin," said a site representative.

The bottom line: Designating protocol numbers, or enabling a method to match shipments with study details on all shipments of supplies and equipment, prevents banishment to the mystery room and, more importantly, ensures that these items are used for the appropriate protocol.

Less is more

As manufacturers minimize product packaging and recycling is accepted as a civic duty, sites say they would like to see an end to oversized shipping containers containing undersized content. "Inside a shipping container that's 3-by-4 feet in size is a single 4-by-5-inch index card and a few bottles of drug," said one staffer. "That's a little bit ludicrous."

One site accumulates so many cold packs that it keeps a container of them in a corridor beneath a sign that reads "Free to a good home" and donates others to a local chocolate shop. Most of the packaging is not recyclable, and space-starved sites are sometimes asked to hold onto it for two years until the study ends.

The bottom line: While shippers for temperature-controlled product may be larger by necessity, in other cases smaller shippers may meet needs and be cost-saving as well. With respect to saving packaging until the study ends, forget it.

Too much of a good thing

Sites frequently receive costly equipment and technology they do not need. Case in point: "We have 12 EKG machines, six of which are identical and two of which are from the same sponsor," one site staffer said. "We have corridors full of EKG machines, but sponsors keep sending them."

And even though this same site has its own state-of-the-art, calibrated temperature-monitoring system, it is using six others that were supplied by sponsors. There are so many temperature-monitoring systems in use, as a matter of fact, that care must be taken to ensure that the sensors do not prevent freezer doors from closing and risk temperature excursions.

The bottom line: If a site already has a state-of-the-art, calibrated piece of equipment, it may not need another. Consult the site about its needs before sending it another costly piece of hardware.

In closing, these issues may be a consequence of addressing supplies as an afterthought rather than a key part of the protocol development process. Historically, supplies have been considered part of the execution rather than the planning phase of clinical trials. Site representatives say it is time to change this and they want to be part of the solution.

They say they are infrequently consulted about the supplies and equipment planned for trials. And when they are consulted, it is often after decisions are in place. By consulting the sites early in the protocol planning process, clinical teams could avoid supply missteps, preserve resources, and make study participation a smoother experience for subjects and sites alike.

Guidelines for planning clinical trials that put volunteers first

Here are some ways in which better planning by clinical teams during protocol planning can create "volunteer-centric" clinical trials—clinical trials that put volunteers first.

- Ask questions of those who know. Investigator site staff can help clinical teams avoid miscommunication and missteps. Sites are a knowledgeable resource and they want to help.
- Consider supplies early in the protocol-planning process. Supplies should be considered part of study planning, not merely execution. Sound decisions about supplies lead to smoother clinical trials and better adherence.
- Put yourself in the shoes of subjects. Clinical teams would do well to walk in the shoes of subjects for the purposes of protocol development. Sites suggest that clinical teams "walk through" the requirements of a protocol in detail before finalizing it so they understand exactly what they are asking of subjects and sites. Another option: Imagine a family member or friend participating in the protocol. Clinical teams should ask themselves these questions: How will the drug look? Will the packaging be easy to open? Are the directions clear and easy to follow? Will the subjects be capable of using the electronic diary, iPhone or other devices? Is what we are asking of volunteers reasonable? How much of a time commitment does this protocol demand? Finally: What can we do better?
- Weigh cost-saving approaches with the end game in mind. Look closely at cost-saving options and consider their impact on the subjects, sites and protocol as a whole. Questions to ask: How could these options impact the protocol? What impact are they likely to have on adherence and/or retention?
- Communicate consistently. Sites need to know what supplies they will receive, the quantity and when to expect them – facts that permit them to do their jobs effectively. Clinical teams would do well to emulate Amazon and Zappos, whose customers are never left to wonder when shipments will arrive.

- One other thing: Once a study is over, subjects frequently inquire about the final outcome. In appreciation for their gift of time, they deserve to know, something that bears future consideration. Volunteers who can point with pride to their contributions could encourage others to participate in clinical trials.
- Keep in mind that everyone has the same goal, that of a successful trial. Sponsors and supply chain managers want to generate clean, reliable data and complete studies on time. Sites share those goals, in addition to the desire to take good care of the volunteers they recruit. And volunteers, who occupy the most important role in clinical research, want to comply with instructions and see the study succeed. “Mutual respect is key,” said one site representative. “We can do this better together, because we all have the same goals.”

About the investigator site panel on clinical supplies

The Investigator Site Panel on Clinical Supplies panel was formed in 2011 and is comprised of global investigator site representatives, clinical supply professionals and industry researchers involved in the implementation of clinical trials in the United States, Europe and South America.

The panel operates on a singular mission: Identify, raise awareness and drive actionable change to the clinical supply issues impacting investigator sites worldwide in order to support improvements in the execution of clinical research and the patient experience.

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