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How to Support & Develop Research - Naïve Clinical Sites

An Investment for the Future of Clinical Trials

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Introduction

Finding highly experienced and strong performing sites for a clinical trial is one of the most important steps in the drug development process, but always remains a challenging task for Sponsors and CROs. The turnover rate of Principle Investigators (PIs) in clinical research is high and keeps rising. Approximately 40% of the global pool of FDA-regulated PIs who file a Form 1572 in a given year choose not to file in the subsequent year. While lower than the other regions, the North American turnover rate is still approximately 35%[1].

Content

This high turnover rate often means you could end up using a site which has little to no experience in clinical research for your study. Using a site new to the world of clinical research is always a risk as they require more time and resources from all involved parties to bring them up to speed with current GCP guidelines and health authority regulations for potentially no return of positive outputs or results. So is using inexperienced sites worth all the time and effort? Our short and resounding answer is "Yes"! While more time and resources are needed to train and develop these sites, we need to look at them as long term investments worth the trouble. After all, these risks can all be analyzed and mitigated at every step of the study. By taking the time and effort to invest in these sites, they are more likely to succeed. You will also be able to build a strong positive relationship with them, and will more likely be able to count on them to perform well, and perform loyally for your future studies. Sites that are well supported and have a solid relationship with the Sponsor or CRO, have better enrollment rates.

> *"it takes all stakeholders in pharma to raise good clinical research sites"*

One of the reasons they are great enrollers is related to the fact that their patient populations are, for the most part, naïve to clinical trial participation. In addition, they do not have competing studies that target the same potential population. The saying "it takes a village to raise a child" applies nicely in this situation… but instead we should look at it as "it takes all stakeholders in pharma to raise good clinical research sites".

Selecting the Site

The Protocol is the very first step where you can start mitigating the risks involved with using an inexperienced site. Each protocol is different and presents its own challenges. The best way to ease new sites into clinical research is to select them for protocols which are less complex.

Take the time to look at the various aspects of your protocol. Some key points to look at include:

- Inclusion / Exclusion Criteria
- Number of Study Related Procedures
- Number of Subject Visits
- Number of Expected Enrolled Subjects from each site

Participating in the first clinical study with complicated procedures would result in confusion, overburden, and possibly withdrawal from further participation in clinical research. Additionally, this will cause more errors and poor quality of data, with a higher possibility of violations occurring, ultimately affecting subject safety. By taking time to identify where in the protocol an inexperienced site might stumble, you reduce the chance of these sites potentially making significant errors. In essence, it's about becoming more "site centric" in your approach. These days there's a lot of talk about patient centricity and how to focus on the needs of the patients throughout a clinical study, and this is wonderful. However, we often forget that the needs of the sites should also be seriously considered when designing and managing a trial.

At Vantage BioTrials, we believe from our own experience that one of the best starting points for these inexperienced sites are Phase IV studies. Phase IV studies will usually have less routine activities during patient visits. The inclusion and exclusion criteria will generally be less stringent, which will help with recruitment. These factors will allow the inexperienced PIs and site staff to become accustomed to the basics of clinical research in a less demanding setting than, say, in an interventional pivotal study. This kind of environment will help set-up an opportunity for these sites to succeed. Of course, inexperienced sites can be used for interventional studies; however it is riskier due to the

higher amount of time and resources a site has to dedicate to these trials. Regardless of what study phase an inexperienced site is chosen to participate in, you must be ready to work twice as hard and communicate closely with the site at each stage of the study.

If an inexperienced site has shown interest in your study, the next step is to perform a site evaluation visit (SEV). The priorities of the site evaluation for these inexperienced sites should be different when compared to one of an experienced site. The most important factors you should look for at the SEV for these new sites are how interested they are in the study and how willing they are to learn. It's about being motivated. A site which is not willing to learn should be avoided as it is a big indicator of unnecessary push-backs and waste of time and resources further down the road.

You should go into the site evaluation expecting them to have little to no clinical research experience or infrastructure. The qualifications of the PI and site staff should be viewed differently between an experienced and inexperienced site. At an experienced site, you might look more at their previous GCP training and experience with other clinical studies. At the inexperienced site, you would focus more on how willing they are to undergo GCP training and how seriously they value training programs in general. The point is: you should not penalize an inexperienced site for their lack of experience! Another example would be site staff resources and infrastructure. At an experienced site, a lack of staff dedicated to clinical research would be a cause for concern as this would indicate the site might be unable to dedicate adequate resources and time to your study. For an inexperienced site, you should look at how they will delegate the study's activities between their available staff. It is important to explain and emphasize how much time and resources the site needs to dedicate to the study as they will have a harder time judging how much resources they need to dedicate. If they are not sure how to delegate their staff to the study, offer them suggestions and examples on how other more experienced sites have set themselves up. As an example, suggest to the site to designate either a nurse or administrator who is in contact with patients a lot as the lead coordinator. While it is not the ideal set-up, as this staff member will have other non-clinical trial related duties, it will allow you and the site one main point of contact for communications. If the site continues to do clinical research in the future, they will develop their resources and infrastructure. Overall, a site evaluation visit should not be done to how qualified these inexperienced sites are to clinical research but to gauge how interested the sites are to participate, how willing are they to learn and to explain to them the necessary time and resources needed to perform the study. Once you have a solid foundation in place, all the infrastructure requirements for clinical research will come with time.

Study Start-up

The start-up of sites is a crucial step of any study and even more so for sites new to research. On average, the start-up phase takes 5 weeks longer for sites new to the Sponsor or CRO, which includes sites new to clinical research, than it does for sites who have established relationships with the Sponsor or CRO2. It is important to get sites through the start-up stage as quickly and efficiently as possible,

while maintaining key study deliverables and decreasing errors. Through the experience we've had at Vantage BioTrials, these new sites are all very excited and ready to start enrolling patients as soon as possible, sometimes even before being selected for the study. The sooner these sites are up and running, the less likely they will lose interest in the study and not meet their recruitment targets, regardless of whether they are experienced or not. Of course, it is very important to remind these inexperienced sites that they have obligations to fulfill prior to starting the study, especially if this is the very first study a site will be taking part of. This should be stated and repeated during the Site Evaluation Visit and Site Initiation Visits. If your study is planning an investigator meeting, make sure your new sites are not only invited, but motivated to attend as this will provide them one or two days of concentrated training and helpful discussions/brainstorming with more experienced sites which they can learn from.

Before the study can start, the regulatory documents must be collected. During the collection of these essential documents from the inexperienced site, it is recommended to explain exactly what documents are being collected and why they are being collected, but to also provide them an outline of the study start-up steps. Providing an explanation on the various steps in the start-up process will ensure a faster and more efficient start-up time for future studies, since a learning curve should no longer exist.

Ethics approval is one of the most time consuming as well confusing steps in the start-up phase for inexperienced sites. If it is possible, the best course of action would be to use a Central ethics committee. The start-up time and enrollment performance is better among sites who are not based in university, hospital and government clinics1. The use of a central ethics board will get your inexperienced site up and running faster, and more importantly, avoid the time consuming and confusing process of going through local ethics committees. As the Sponsor or CRO, you will also be able to take the burden off the shoulders of the site and they will have one less thing to worry about since central ethics committees are usually managed directly through you (not the site). If you have to use a local ethics board, you have to be ready to walk step by step with these inexperienced sites through the approval process and guide them on timing of submissions and general communication with local committees. More experienced sites will be able to do the submission process with minimal intervention, but with inexperienced sites, this process can be confusing to know even where to start.

For local ethics boards, it is important for both the site and you take the time to learn how the ethic boards work. If you have an experienced site in your study using the same ethics board as your inexperienced one (which can be a normal situation within the "streamlined IRB process" we have in several Canadian provinces), have the experienced site act as the primary site if possible. This will help your new sites learn about the approval process while avoiding delays and making preventable mistakes. Surveying veteran sites on their past experience and challenges faced with their local ethics board submissions could be another affective way to gain a helpful insight. Another great way to help inexperienced sites through the approval process is for you to learn from experienced sites about their experiences using the local ethics board. The experienced sites will have better insight into the inner workings of these ethics boards, what they look for and their timelines. Ask these experienced sites and as well look up on the ethics board website to learn what needs to submitted, as each ethics committee

is different. While this process might be time consuming for you, you will be better positioned to help your inexperienced sites though the approval process for this study and all future studies. For the actual submission, it is recommended that you try to schedule a time to do the submission process together with the site, either remotely or in person. By doing so, the sites will be able to provide a more detailed submission to the IRB and both you and the site will learn how the IRB works. A more detailed submission will mean fewer follow-up questions from the IRB and a faster start-up time.

For site training, always recommend to the PI and site staff to attend the Investigator meeting. This not only provides these sites a chance to meet with you in person to discuss their comments and concerns with the study, but also to meet the more experienced PIs. This opportunity gives these new sites a chance to look at the study from a different perspective. The experienced sites will more likely catch details within the protocol that inexperienced sites might not notice which could potentially affect enrollment. Conversely, you would be surprised at the great level of insight and input that also comes from your inexperienced sites at investigator meetings since they might have more "real world" experience with patients than clinical setting experience of seasoned sites. If attending the IM is not possible, then an on-site training visit should be performed. If the site has to do any additional training, such as GCP training, have them do it before your site visit. This will allow them to ask questions to you in person. During this training visit, recommend to the PI to be present for as long as possible. While it might not be feasible, the more time the PI spends with you during the SIV, the more prepared for the study the site will be. In the author's experience when performing an SIV with an inexperienced site, the PI was present for most of the SIV and that allowed them to ask questions about all aspects of the study in a more leisurely fashion. This not only allowed the site to be better prepared for the study but it allowed the author and the study team to look at the study from a new perspective. By the end of the SIV, the PI and the site should be comfortable performing the study related activities and be comfortable coming to you for questions regarding the study.

Open and Responsive Communication Throughout the Study

The most important factor to ensuring success of inexperienced sites is communication. Communicating with your sites is fundamental in every study to ensure its success. For inexperienced sites, it is even more important to be open to communicating with them at every stage of the study. These sites will usually have a lot of questions on various aspects of the study, whether it is general or study specific. It is important you emphasize to the sites you are always there to answer their questions and to help them. Recommend to them to call you prior to their first subject enrollment just to go over the summary of a subject visit. It is recommended you monitor these sites early in the study. By doing so, any mistakes can be corrected early on and will save time and effort later on in the study by decreasing the potential number of data queries or deviations. As well, if possible, allocate more monitoring visits to these sites. In the author's experience, these sites are very receptive to monitoring visits as most realize that it is in their best interest to learn as much as possible from experienced personnel. It acts as a learning

experience for the site and encourages them to do well. Do not be afraid to be thorough with these sites. For a Phase IV study the author recently worked on, one inexperienced site told the author that they welcome on-site monitoring visits, as it allows them to learn what they are doing well, what they are doing wrong and how they can improve. They were very open to feedback and very enthusiastic about improving their processes. By pointing out areas of improvement but at the same time highlighting their strengths will in turn result in a positive and successful clinical trials experience, and improve the quality of their work. By being open and responsive to the site's questions, an inexperienced site will know they are being supported throughout the trial and will more likely participate in future trials as their confidence grows.

Clinical research is always a risky endeavor. The prospect of having to use inexperienced sites will add to this uncertainty. There are a lot of unknown factors at play which could end up affecting your trial. But these inexperienced sites are not only important for your trial, but for all clinical trials. With such a high PI turnover in clinical trials, it is essential to do as much as possible to retain as many new PIs and sites as you can. After all, we need patients to enroll in clinical studies in order to advance research, but similarly without a growing pool of sites, the advancement of breakthrough research can also slow down, or worse, stop altogether. By knowing when to select a new site and by providing close and responsive support to these sites, you will not only allow the site to have a successful clinical trial experience, but you will build a strong positive relationship with them which you can tap into for future studies. It's time we all do our part as Sponsors and CROs and turn an unsustainable system into one that continuously produces and maintains top quality sites. And that is an investment worth taking.

Contact us at Vantage BioTrials today to learn more about how we can support your clinical programs by developing long lasting relationships with sites and speed-up the entire study process while maintaining the highest levels of quality.

About the Author

Robert Le is a Clinical Research Associate at Vantage BioTrials, Inc. He works closely with sites in successfully completing Phase I through IV studies, and has a strong passion to see that promising new therapies are delivered to patients who need them the most.

About us

Founded in 2007, Vantage BioTrials is a privately-held Contract Research Organization (CRO) that provides Phase I-IV clinical trial management services and implements Risk-Based Management through the use of Quality by Design (QbD) methodologies, all delivered to international pharmaceutical, biotechnology, generic pharmaceutical and medical device companies.

To learn more about Vantage BioTrials, please visit us at www.vantagebiotrials.com and follow us on LinkedIn and Twitter.

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