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Fighting the Commoditization of Sites: It Starts with the Site Initiation Visit

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Despite advancements in clinical research technology over the last decade, recent research from the Tufts Center for the Study of Drug Development (CSDD) suggests that we are not conducting site activation any faster today than we did 20 years ago. One of the biggest factors contributing to lengthy cycle times is the inability of sponsors and Contract Research Organizations (CROs) to engage investigative sites in a manner that supports effective patient recruitment and retention in the context of a swift budget and contract process. In this mentality, the site is treated less like a valued partner and more like a commodity in the clinical research lifecycle. Want to move towards better engagement models? It starts with the Site Initiation Visit (SIV), a critical event that sets the stage for an open, collaborative relationship to last throughout the study. An initiation visit is imperative to the overall success of a study as many crucial tasks are accomplished during these visits.

The SIV defined

A Site Initiation Visit (SIV) is required to prepare and set up a research site to conduct a clinical study and needs to occur prior to patient recruitment and site activation for a specific protocol. During the SIV, the clinical study team receives a thorough training from the study sponsor or CRO on the study protocol.
These visits have several goals:

1. to orient and train staff on the protocol and study related processes;
2. to confirm readiness for study implementation;
3. to identify additional requirements that must be satisfied prior to site activation and subject recruitment.

The Principal Investigator (PI) must attend the SIV, together with as many members of the study team as possible. The initiation visit usually occurs after the site has completed all regulatory requirements, budget and contractual requirements, and has obtained Institutional Review Board (IRB) approval for the research study at their site. The initiation visit is the last step before the study site is activated for enrollment.

With so much at stake, what are the essential elements of successful SIVs? And what are the common pitfalls to avoid?

Essential elements of the SIV

In working with CRAs and field staff over the years, I have learned that best practices for ensuring a quality SIV involves careful preparation, tailored delivery of the content during the visit, as well as post-SIV follow-up.

Preparation tips

- The SIV should be scheduled **close to the anticipated activation date** so information discussed at the visit is retained by the site staff.
- **All departments** that are involved in procedures for the study should be contacted so that they have the opportunity to attend the main initiation visit, or to schedule time for a visit from the study sponsor or CRO while on site.
- A full agenda should be sent out to the study site prior to the meeting, and **all essential documents** should be in place prior to, or collected during, the meeting.
- All **study supplies** should have been ordered and be **on site** for this meeting.

During the SIV

During this meeting, the study sponsor or CRO spend a lot of time training or reviewing the study protocol design, and answering questions from the site study team personnel. Discussion typically centers around the study protocol, especially the inclusion/exclusion criteria, study procedures, and the potential research participant's pathway. Discussion also occurs about the monitoring plan for the study – including safety reporting procedures and monitoring, as well as Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) requirements. It is also the opportunity for the sponsor or CRO to ensure that the PI fully understands their responsibilities (21 CFR 312 Subpart D).

"The propensity is to believe that when a 1572 has been signed, the relationship has been inked – and quality should just follow," says Christine Pierre, President of the Society for Clinical Research Sites. "In reality, quality clinical research requires ongoing dialogue- Is the protocol practical? Are supply shipments supporting protocol compliance? This delicate interplay must continue between the sponsor, the site, the CRO and all of the vendors on the study. The willingness to treat the site as part of the partnership as opposed to a means to the ends moves the focus from a commodity transaction to a true partnership. True partnerships benefit all the parties and with this unified and valued relationship all benefit."

Goals of the SIV: What to achieve:

- Ensure that all investigators and site study team are fully informed of their **roles and responsibilities** and obligations regarding the trial
- Full preparation of site to conduct the trial according to the **Protocol and Good Clinical Practice (GCP)**
- Review **study overview, eligibility criteria, procedures,** affirm access to suitable patient population
- Use and maintenance of the Investigator Site File. Previously unsigned agreements will be obtained (CTA, FDA 1572, Financial Disclosures, etc.)
- Ensure that **site staff is trained on the protocol** and responses to questions provided in consultation with study team
- Reconfirm the **proper set up of study procedures** at site for trial execution
- Review **safety reporting** procedures
- Discuss requirements regarding **source data verification** and **minimum medical record** entries.
- Review **timing** and **requirements** for **monitoring visits.**
- The role of any **special investigations or procedures** used during the course of the clinical study, e.g., use of central labs, diagnostic tests
- Re-verify nothing has changed since site selection that may impact the **availability of adequate facilities and resources** at site to conduct trial
- Verify that all study **supplies** are in good condition, fully operational and within expiration dates
- **Data handling and electronic systems** training is complete

It is important that all study related training is well documented, and this documentation should be placed in the sponsor's Trial Master File (TMF).

Common pitfalls to avoid

It is important to understand the SIV is more than just a checklist of tasks to complete. To avoid commoditization of sites, there are some issues to keep on your radar.

1 – Use of remote SIVs when it is not appropriate

During study start-up, a sponsor may choose to hold a remote initiation meeting for a large number of sites in lieu of conducting many site initiation visits. This will obviously save money, but for complicated studies, the opportunity for study team members to come together face to face with the study sponsor or CRO and brainstorm for several hours during an on premise SIV is invaluable. Not all sites are good candidates for remote or virtual SIVs. Factors such as site's research history, location, availability and knowledge of the staff are key considerations to think about before deciding to go virtual.

2 – Training that is too generic

Training provided by sponsors can be generic, lacking role-based specificity. This high-level training can often be repetitive and ultimately wastes time. It can also leave the site with a greater number of data queries, findings from monitors and potential protocol deviations. Protocol complexity also plays into this issue. Are some sites more likely to misunderstand aspects of the protocol due to culture, norms, or general practices? Again, not all sites are the same, so your training plan must adjust accordingly.

Beth Harper, President of Clinical Performance Partners, stated, “Recognize that all sites are not created equal and adjust your training to the needs of each site audience who have different levels of knowledge and experience. All too often SIV’s follow a standard “death by PowerPoint” slide presentation approach that doesn’t serve anyone well. Identifying in advance, the key areas for each site that are not clear and providing the opportunity to simulate as many of the challenging aspects of the protocol through hands-on activities are highly effective techniques for ensuring the training is relevant, effective and matches the needs of each site.”

3 – Lack of communication with the site

The site too has a part to play in making the SIV successful. Sponsors may not be aware of a site’s start-up process and, if communication is not maintained, the site may not receive all the information and tools it needs to begin the study. The site has an obligation to be proactive and provide information to the sponsor about the tools and information it needs to get started – prior to the SIV.

After the SIV

After the SIV, a site initiation report should be completed by the designated CRA. Depending on the SOPs for the study, the sponsor may need to review the report prior to its finalization. Once finalized, the original report should be filed in the electronic Trial Master File (eTMF) as well as in the investigator site file. A follow up letter should be sent to the investigator detailing any decisions or key issues covered. Copies should also be sent to all appropriate site staff.

According to 21 CFR 812.110, the ultimate responsibility is on the investigator to provide oversight and ensure that the study staff executes the study according to federal regulations, agreements between the sponsor and investigator, investigational plan, and requirements of the IRB. In practice, site-sponsor engagement is a critical success factor. Delivering a robust SIV that is well-planned and appropriate for the site, given its history, working relationship, knowledge, resources, and culture, is the first step in the road to successful execution.

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