Site Management in the Era of ICH-GCP E6 R2

When the new ICH-GCP E6 R2 revision came into effect on June 14, 2017, the European Medicines Agency (EMA) was the first among three agencies (Food and Drug Administration, EMA and Pharmaceuticals and Medical Devices Agency) to implement this updated regulation. The E6 R2 revision is long in the making, and it implements some of the requests that have been made by legislators throughout the last decade. Among these, particular importance and emphasis is given to investigator and sponsors' oversight duties.

Principal investigators are reminded of their critical role in delegation, oversight and conduct of clinical trials at their sites. In parallel, in the heavily outsourced world of clinical trials, sponsors are now responsible for larger and more insightful oversight, covering not only the parties they directly outsource to, but also any subcontractor or third-party vendor. Furthermore, a more comprehensive risk-based approach is requested with the aim of preventing systematic errors rather than only correcting issues that have already occurred.

Oversight of clinical sites now becomes an even more important topic than in past years as it is key to any successful global clinical trial. The first step to achieving effective oversight of clinical sites is through site selection and feasibility. Choosing the right site (i.e. with the right resources and the right patient population) is critical to reducing the level of errors and increasing the quality of the clinical data collected. After the right sites have been selected, it's advised sponsors use a multi-pronged approach to ensure sites are, and remain throughout study duration, engaged and that proper oversight is provided in accordance with the new guidelines. Below are key factors for sponsors to consider:

Regularly Train Site Staff

The first pillar in my approach is to provide regular training for site staff. This can be done through a variety of means, such as specific onsite or remote training (e.g. webexes). Training specifically aims to explain the key and critical points within the protocol, as well as procedures based on an in depth risk analysis of the clinical trial.

It is important to focus on the critical points and consistently deliver the same message to avoid dispersing the message itself. Indeed, I have found that such a focused approach helps prevent errors and protocol deviations that were the "norm" when more generalized training

is provided. In this respect, pharmaceutical companies are today moving towards mutual recognition of some of the "housekeeping" (e.g. ICH-GCP refreshers) needed, thus allowing an even more focused delivery of training on the protocol and critical points.

Building Strong Site Relationships

The second important pillar in building a successful strategy lies in the relationship with sites. Investing into this relationship is very important to maximize both data quality and speed of recruitment. Sponsors will always be a preferred point of contact for sites, regardless of their relationships with CROs. It is critical for sponsors to ensure they are present and visible to all sites whenever possible.

Furthermore, sponsors should create a dedicated professional figure (Site Liaison Manager) and work closely with their CRO partners to attend site selection visits, site initiation visits or any other site visit. This is crucial in order to foster a strong relationship and bond with site staff. This allowed me to support sites as needed and provide real insight into their activities and needs. These visits have also been the opportunity to provide, for example, training and/or specific answers to recruitment questions, thus reinforcing our strategy on delivering focused training.

Quality Control

The third pillar of an oversight strategy is represented by its mechanisms (e.g. quality control and quality assurance). Next to the usual tools (eTools and more standard tools), I have specifically implemented a Clinical Operations Quality Control function. This differs from the usual work provided by clinical research associates (CRAs), as it is, in essence, oversight of the CRA's work. This activity has the aim to correct and prevent errors, as well as issues in monitoring activities in a study, and across different compounds and clinical developments. It includes a mixture of remote and onsite sponsor oversight; it is not outsourced to any external vendor, but is conducted by contractors or full-time employees with a long experience in monitoring and project management.

Such an approach can raise some concerns by the CRO. Therefore, it is important to coordinate very closely with your partners and ensure there is full understanding among all parties. This is not simply a control mechanism, but rather a coordinated effort to improve

quality and prevent errors (especially future and systematic errors across different developmental projects and clinical trials), while ensuring the clinical trial delivers on its endpoints.

Additionally, it should be mentioned that this approach will only work if the technology "feeding" it is fit for purpose. Incomplete or delayed data will cause the approach to be ineffective and ultimately fail its purpose. Finally, this quality control mechanism does not replace the traditional and very distinct quality assurance mechanisms (e.g. site audits). They are instead complementary and should have a constantly open communication channel so that one can "learn" from the other and address efforts where needed (e.g. critical areas or areas where frequent errors have been found).

Creating a Holistic Approach to Data Collection

The fourth pillar in a comprehensive approach to site management is represented by a holistic view of study systems and data. The main focus should be on the trial master file (TMF), but really a holistic approach is critical for successful management of sites. Indeed, data coming from the IXRS, any CTMS, laboratory databases, any other system used on the clinical trial, and even any tracker, should be easily accessible to the relevant team members. Furthermore, it should be discussed altogether in a multi-disciplinary team meeting.

These data are that will be used for a successful risk management approach. What's more, the data will drive early corrections and preventions of errors; they will also dictate the tolerance limits needed for efficient monitoring. Clearly, for this to work implies the data are evaluated in a dynamic and continuous way (trends rather than snapshots) against key performance indicators (with well-defined tolerance limits). It is important to underline that this can only be done in a multi-functional team, and it should not be simply delegated to project management alone. This is a team effort.

Conclusion

In summary, we have defined four main pillars to a comprehensive and successful approach to site management. The suggested approach aims to fulfill the sponsor duties, but it also aims to really improve the overall clinical trial performance and efficiencies. In fact, data is at the core of patients' well-being and safety, and, at the same time, of any successful

developmental program. The key point in this approach is to build strong relationships with all site staff. They are the engine of clinical trials and play a critical role in such respect. They are essentially key stakeholders. Therefore, it is important to invest heavily in building these relationships and not necessarily delegate them in full to our CRO partners.

However, for any approach to be successful, it needs to be shared and understood by all parties. This implies that coordination and full agreement with our vendor partners is key to bringing the desired results. Finally, successful management and oversight of clinical trial sites requires multi-functional support internally to the sponsor, and optimal overview on all key performance indicators at all times throughout the study conduct. Without a holistic view on all trends and indicators, errors cannot easily be prevented. Therefore, we would miss once more the indications in the new ICH-GCP guidelines – quality by design or preventing rather than correcting.

References

http://www.appliedclinicaltrialsonline.com/site-engagement-key-running-successful-clinical-trial