Self Improvement

It's time to call a halt to self-auditing of clinical trials to overcome a conflict of interest and drive improvements for sponsors. A move to more independent, proactive audits would be a 'win-win' for the industry

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As clinical research organisations (CROs) have proliferated, so has the fact that they frequently carry out good clinical practice (GCP) audits themselves. Yet it is difficult to understand how this critical data can be audited by the very same organisation that has created it. Aside from the obvious conflict of interest – or perhaps because of it – self-auditing rarely improves the process of completing a clinical trial.

Given the amount of data collected, and the fact that auditors are on site, routine audits should lead to an intelligent analysis of how to improve trial delivery, but this rarely happens with the self-auditing approach.

To tackle this issue, the industry should look towards the use of independent, external auditors, as well as smaller, more proactive GCP audits that consider the process as well as the findings – with the results fed to sponsors to help improve their internal process, increase effectiveness and lower clinical trial costs.

Failing to Fix Problems

Drug development without clinical research is like baseball without a pitch, or cricket without a wicket. It might work, but it is challenging to figure out what it would look like. As such, effective clinical research is critical. But despite this imperative, clinical trials can be conducted poorly and fail for many reasons, leading to money being wasted, lost time and, worst of all, delays to potential cures and treatments for patients.

Some trials might fail due to a lack of efficacy and safety – faults which cannot be corrected during the study. Others might fail due to poor design, management and monitoring – issues that may be fixed but all too often are left ignored (1). Consider the following hypothetical scenario:

A sponsor plans and begins a multicentre trial on a new diabetes drug, utilising 80 sites around the world. A large CRO is selected to manage the trial, in part because it has contacts and monitors in every relevant country. This CRO also offers auditing services and, as is often the case, bundles these components together so that the sponsor selects the entire package.

As the clinical trial moves forward, the CRO's monitors begin to notice that the informed consent forms are not completed adequately. Some of the monitors take note of this, others do not. As the trial progresses, they continue to notice this problem, but since the CRO is large, the issue is never raised at a level senior enough to reach the client.

At some point, auditors are dispatched to evaluate how well GCP is being followed during the trial. The auditors produce a report that is generally favourable. They criticise the monitors lightly, but do not go beyond that as they know the monitors and do not want to offend them. They do not raise the issue with senior management to avoid causing any trouble at corporate headquarters.

Negative Implications

There are several outcomes from this scenario. Clearly, the fact that the informed consent is incorrect is a problem – one that could lead to difficulties for the sponsor with the Food and Drug Administration or the European Medicines Agency. When the trial is audited by a regulatory agency, the sponsor will be shocked to discover the irregularities. Hopefully, the lack of informed consent will not delay approval; however, the image of the trial will arguably be tainted in the agency's mind.

Furthermore, there is always the possibility that a reviewing agency will disqualify a particular site and mark it as useless. This could potentially prevent the trial from reaching its statistical endpoint, resulting in wasted money and the derailment of a lifesaving product as a result of this lack of independence.

Of equal concern in the long term is the lack of information the sponsor may have received concerning its trial. Recent publications have highlighted the fact that, despite the existence of quality systems, CROs and sponsors often miss critical improvement points (1). A 2009 article demonstrated that a single audit at database lock is insufficient to maintain quality; researchers at Duke University have found that a series of small audits that provide ongoing information is more effective (2).

Conflict of Interest

But the industry does not change. And it does not change for all the wrong reasons. There is an inherent conflict of interest when CROs audit the same trials that they are monitoring. It is hard to imagine that a lone GCP auditor, employed by a major CRO, is able to objectively assess the work conducted

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by its employer. Furthermore, when compliance issues are found, it takes courage for the auditor to bring these to light for fear of jeopardising the reputation of the CRO.

Most people consider information about their money and their health to be extremely important. In recent years, the enactment of the Sarbanes-Oxley legislation in the US has made it clear that commingling the creation of a firm's financial statements with the same group doing the financial auditing is not allowed. Yet this practice remains standard in the clinical trial realm.

Of course, there has been no clinical trial version of the Enron scandal, and no far-reaching issues have been uncovered as a result of pharma self-audits. But this does not mean the practice is right, or that it should continue.

Valuable Information

There are two reasons why self-auditing should stop. Not only is the perception of a conflict of interest problematic, but the reality of information flow is troubling. Sponsors are being shortchanged in their desire to improve the clinical trial process as a result of the current audit systems.

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Aside from obvious protocol issues, the types of valuable information that can be gleaned from an effective audit include:

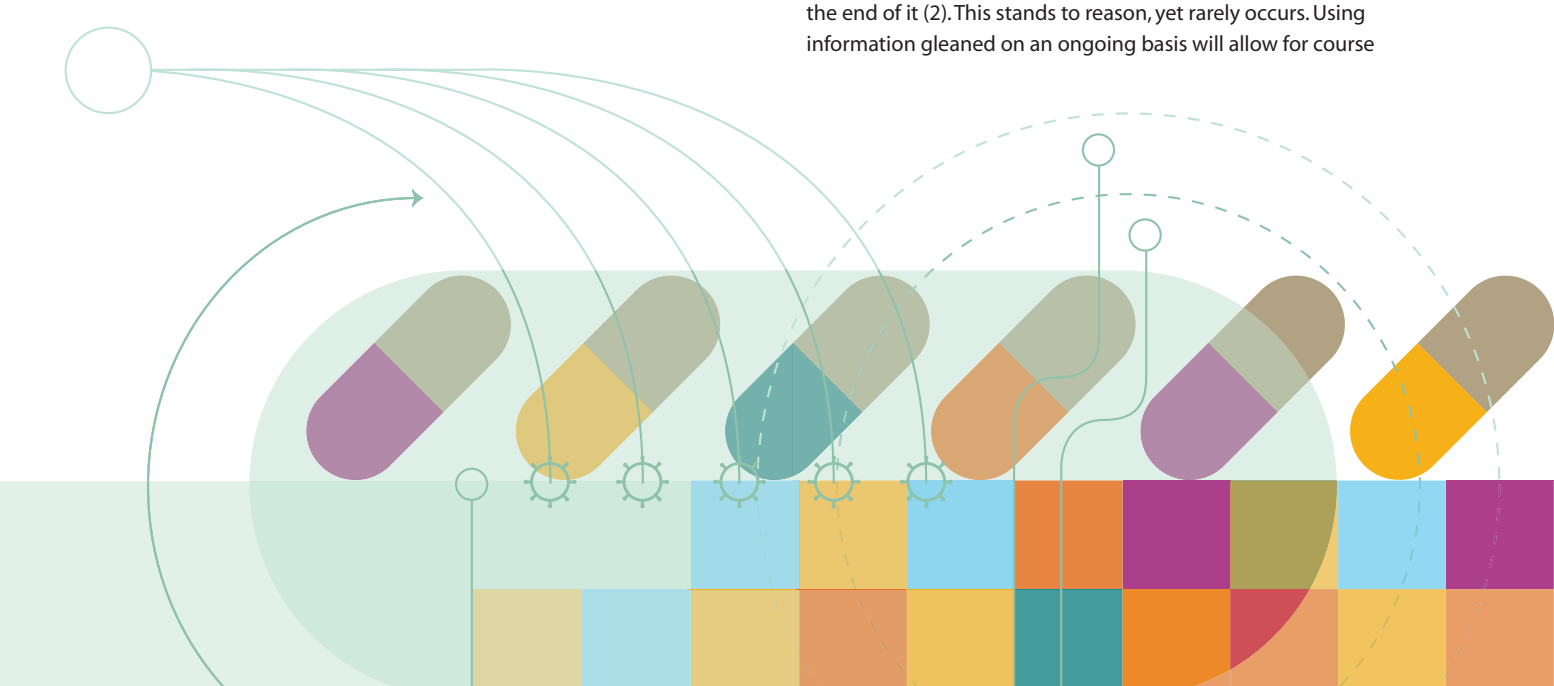
- Was the investigator/staff engaged, knowledgeable, capable and professional? Is this a site that should be used again?
- Was the site well organised? Could it withstand the rigours of a regulatory agency audit?
- What did staff at the site think of the protocol and the process? Often the people doing the work have the most insight into how the process could be improved
- Were the sponsor's computer systems capable and useful? As many sites work for more than one sponsor, is this trial's information technology easier or harder to manage?

These issues are never really raised during self-auditing, but they should be. The industry's thinking should change. Audits should be seen as both proactive and reactive. Necessary changes include the use of independent auditors and a desire to learn more about the trial than just GxP compliance.

Proactive Audits

Audits are not really used proactively in the GCP realm. Interestingly, on the manufacturing side of the firm, good manufacturing practice or quality systems audits are routinely used in a proactive sense. Medical products companies have learned that the information gained from an audit has much more to offer than just compliance. The clinical side of the organisation should take note from these efforts.

As mentioned above, a Duke University study discovered that a series of small audits conducted during the course of a trial can yield far more useful information than a large audit at the end of it (2). This stands to reason, yet rarely occurs. Using information gleaned on an ongoing basis will allow for course



correction, evolution of informed consent, and changes to future protocols. Managers in the clinical setting will be able to improve trial productivity, patient retention and even recruitment, by studying the process of the clinical trial. Audits are the best mode of providing that information.

An obvious reason why proactive GCP audits rarely occur is that audits are almost always seen as a cost, not as a benefit. When a series of audits is commissioned by a sponsor, the main issue for the auditor is cost, not value. Sponsors see audits as a necessary evil, not as a useful tool. This perception leads to a loss of information and, ultimately, a less-than-effective process.

Future Improvements

If sponsors were to value an audit for its ability to provide useful data – and value the audit report as a mechanism for information exchange and process improvement – the perception of clinical trial audits would change. By itself, this may not impact audit costs directly, but more audits may be completed, even shorter ones. This would allow sponsors to improve the process and eventually lower the expenditure necessary to complete a trial. Improved effectiveness would also save money in the long term.

To put this all in a neat box, consider the hypothetical scenario outlined above. Instead of the CRO auditing itself, an outside auditor, commissioned to consider the process as well as the findings, is engaged. Early on, the auditor discovers the lack of monitor involvement and identifies the issues with the informed consent and trial site follow-up.

The sponsor is able to push the CRO to do the contracted job and issues a new version of the informed consent. No suspicions are raised at the regulatory agency, and the sponsor is able to use this information in its next clinical trial, thereby allowing future improvements. Money is saved, management is pleased, and everybody wins.

References

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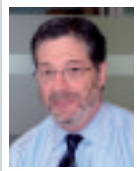
About the author



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