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Clinical trial fraud: Mitigating risk with a compliance program framework

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The recent spotlight on the pathway to vaccine development during the COVID-19 pandemic has heightened discussion around science, clinical trial processes, clinical data collection, and the data used to support vaccines and other drug development. Political discussions on the vaccine debate aside, clinical trial conduct may seem secretive and, at times, perhaps not transparent to those unfamiliar. Questioning science and clinical trials hints at underlying implications of fraud or misconduct. However, clinical trial fraud or, more appropriately called, research misconduct, is not a new topic that came with the fury of clinical trial research during the pandemic. In the last few years, clinical trial fraud has been at the forefront of many highly publicized cases brought by the Department of Justice (DOJ).

In December 2021, at the Food and Drug Law Institute Conference, the DOJ announced that clinical trial fraud would be one of four enforcement focus areas for the agency. The announcement delivered by Deputy Assistant Attorney General Arun Rao highlighted the work of the Consumer Protection Branch of the DOJ around the importance of protecting Americans' health, safety, and economic security.[1] The Department of Health & Human Services' Office of Research Integrity (ORI) defines research misconduct as "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results."[2] Research misconduct can include omitting, altering, fabricating, or broadly interpreting clinical data. This can happen when a researcher conducts a clinical trial, during the design of the clinical trial by a sponsor, during data recording within a clinical trial, and when someone supervises or reviews the research taking place. An individual can also commit research misconduct when results are reported either to a public registry or a clinical trial sponsor. This article will discuss notable past enforcement actions by the DOJ to highlight the ways in which clinical trial fraud may appear and ways that clinical trial sponsors/pharmaceutical companies can mitigate the risk surrounding clinical trial fraud in their compliance programs.

Notable enforcement actions

In and of itself, clinical trial fraud does not carry criminal penalties or jail sentences; however, it is often the case that defendants in clinical trial fraud cases have also been found to violate the False Claims Act, commit wire fraud when operating across state lines, and violate the Anti-Kickback Statute. In many cases, uncovering fraud within a clinical trial can levy heavy financial fines against individuals, companies, and universities.

In 2019, the Attorney's Office for the Eastern District of Washington brought a case against an individual and the clinical trial centers he owed for falsifying clinical research data in connection with a fraud scheme.[3] The centers conducted trials to treat a wide variety of medical conditions, including mental health conditions, heart disease, and opioid addiction. The case was shocking for several reasons, including the crimes themselves and the fatal outcome for two trial participants.

An immigrant to the US, the trial center owner was unable to obtain the required US license to practice medicine;

instead, he became the owner of several clinical trial sites. According to the DOJ, he made over $6 million from pharmaceutical companies to conduct clinical trials. The compensation the clinical trial centers received were the result of the owner's enrollment of participants who were otherwise ineligible or excluded, falsification of participant medical records, and illegal collection of samples from unwilling or unsuspecting subjects of a trial.

Ultimately, the clinical trial owner received a significant jail sentence and a monetary judgment against him of $1.9 million. However, the harsh reality is that the public was put in considerable danger because of his actions which ultimately led to the deaths of two participants.[4] One participant was a pediatric subject who was misdiagnosed to be included in a clinical trial and the second was a subject who had been enrolled in multiple clinical trials without appropriate monitoring.

In two unconnected cases from Florida, jail sentences for three individuals—a principal investigator, a study coordinator, and a clinical site director—equaled more than 120 months in jail and $2.1 million in restitution after the DOJ uncovered their schemes to defraud pharmaceutical companies financially. Each individual committed clinical trial fraud by falsifying clinical trial data and reporting that participants received study drugs when they had not; however, when they accepted payments—the transmission of which crossed state lines—for fraudulent activities, the DOJ included wire fraud charges.[5][6]

While these cases demonstrate some of the extreme outcomes of clinical trial fraud, other examples highlight that clinical trial fraud is not only found within the private clinical trial sector. For instance, in 2019, a Duke University lab employee reported that another Duke University researcher falsified clinical data and medical research to obtain federal grant money from the National Institutes of Health and the Environmental Protection Agency. The fraud occurred undetected for more than 15 years and resulted in the award of close to $200 million in research grant money to the university. Duke University agreed to pay $112.5 million to settle the False Claims Act allegation by the whistleblower.[7]

A compliance program framework to mitigate clinical trial fraud

There is too much at stake for the public and the pharmaceutical industry for clinical trial sponsors not to invest time and resources into comprehensive compliance programs that can identify, investigate, and address research fraud in clinical trials. While the motivating factors are not apparent in the cases mentioned, what is clear is that the outcome can be death for research participants. Other impacts of research fraud include a lack of faith in medical research and "may serve to undermine confidence in the healthcare industry as a whole."[8] Medical advancements and progress can also be slowed across therapeutic areas to find treatments as a result of clinical trial fraud.

Truly successful compliance programs include two fundamental components: the development of a comprehensive compliance framework and dedication by those within an organization to adopt the program. The challenge to a compliance program around a topic like research fraud is that the implication of fraud generally rests with the principal investigator or their staff and that routine monitoring by the trial sponsor is enough of a preventive measure to guard against research fraud in a program. Unfortunately, routine monitoring in and of itself may not be enough. Other elements of a compliance framework can supplement monitoring of patient safety and mitigate data integrity risk. So, where does the risk lie, and what framework could a clinical trial sponsor consider putting into place to address it?

Investigators and sites

The first area of risk to consider is the investigators selected to conduct the clinical trial, the clinical trial site, and the staff supporting the investigator during the trial. In many of the enforcement actions discussed in the

examples above, there appear to be a few key players in each case: the investigator or researcher, the study site director, and the supporting study staff. Individuals in these roles have the access needed to falsify, omit, or alter data at the site level throughout a clinical trial. These roles are also directly connected to clinical trial sponsors when reporting data.

One way to mitigate risk around investigators and sites is to prescreen potential investigators and the trial location and conduct a feasibility assessment. A simple tool to support this is to create a questionnaire that supplements standard experience and capability assessment questions of both the investigator, subinvestigators, and the research site. For example, a sponsor may ask whether the investigator, any of their staff, or the site itself has been debarred, has had a related license suspended, or is excluded from participating in federal healthcare programs. In addition, the sponsor should require the prescreening to be completed before any investigator or site is approved to participate in a clinical trial.

Clinical trial/research agreement legal terms

The second area of risk to consider, or where trial sponsors can mitigate risk, is in its legal terms within written agreements between a sponsor, investigators, and sites. Three key sections that can prove beneficial to mitigating risk up front are the inclusion of specific compliance with laws section, a debarment and investigations section, and an auditing and monitoring section. The following are some components a sponsor may consider adding to their template.

- In a compliance with laws section, include language that requires the principal investigator to comply with regulatory health authority forms like the Food and Drug Administration Form 1572, Investigator's Statement.
- Include explicit language that requires confirmation that an investigator, the staff, or the site are not debarred, have not been debarred, and are not currently under any investigation related to debarment, misconduct, or the like. While many might not agree with disclosing investigations that have not yet been substantiated, this could save a sponsor from unnecessary risk in the long term.
- Add auditing and monitoring language to allow a sponsor to access the facility to conduct on-site monitoring and auditing. While the concept seems simple, investigators may not be so eager to let someone in and start looking under the rug in a for-cause situation. Therefore, it is best to have that in a contractual agreement up front.

Sponsor and clinical trial site staff training

Training is a third area where risk might be mitigated around clinical trial fraud. Like any successful compliance program, a program cannot be successful if those affected by the compliance requirements are not aware of the policies and procedures. Regular and routine training should be a staple for internal clinical trial sponsor staff who are designing, developing, and executing a clinical trial, as well as external investigators and study staff, and any contract research organization (CRO) vendors that a sponsor may use.

The first opportunity for a sponsor to provide training for investigators and their study staff is often at the site initiation visit (SIV) or the investigator meeting (IM). The SIV or IM is a chance for the sponsor or their CRO to conduct training in person, when possible, and be able to answer any questions investigators or study staff might have about the expectations, rules, regulations, and policies of conducting a clinical trial. It should not be taken for granted that experienced clinical trial investigators know all the expectations, rules, or policies. It also does not hurt to always provide a refresher. A key topic to consider as part of these site trainings is often referred to as whistleblower training. This training should identify what research misconduct is, ways to identify misconduct,

and ways to report the misconduct to the sponsor of the study. The topics within whistleblower training can also be valuable for sponsor employees and staff to recognize research misconduct as they make contact with clinical trial data from sites or if they receive information from site staff about allegations of misconduct.

Monitoring and auditing

The fourth area of risk mitigation is monitoring and auditing. Our compliance role is only half done when we publish policies, procedures, and training. The other half of a successful compliance program is monitoring and auditing to ensure that the day-to-day work of individuals and groups implements policies, procedures, and training.

The COVID pandemic taught us that there are things we can do even if we cannot meet in person; monitoring clinical trials has been one of those things. Where possible, many sponsors have identified ways that they can monitor clinical trial sites and activities remotely through a variety of methods. However, the flexibility of remote monitoring should not substitute all monitoring when it can safely take place. Developing and implementing monitoring and auditing policies for clinical trials are critical requirements of any clinical trial program conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and other health authority guidance. Within those policies and procedures, clinical trial sponsors may consider a tool like a clinical monitoring plan that provides a working guide for clinical trial sponsor staff and the CRO that outlines the elements necessary to perform monitoring and data review at an investigator site. The clinical monitoring plan's key elements might include standard operating procedure listings, training plans, communication plans, operational guidelines, regulatory document collection processes, site visit reporting requirements, and detection and handling of suspected fraud. Another tool to consider is developing an oversight plan of monitoring activities. For example, when a clinical trial sponsor uses the services of a CRO to manage its clinical trials, which includes monitoring, the clinical trial sponsor should take steps to establish oversight of the CRO's monitoring activities and ensure gaps are closed.

Report fraud/misconduct to authorities

A final area of risk mitigation that should be a part of any clinical trial fraud compliance program is enforcement. Many sponsors may not carry through the reporting of the fraud. For example, a sponsor may investigate potential fraud in its trial, find the fraud allegation to be founded or at a minimum plausible, terminate the site from the study, and move on. While that does insulate the sponsor from future risk with that one investigator, if the sponsor does not report the fraud to the relevant health authorities, there is a chance the fraud will continue with another clinical trial, which could have severe consequences for the public's safety. Therefore, reporting clinical trial misconduct to relevant health authorities should be the standard procedure.

Conclusion

Research misconduct or clinical trial fraud is often not the bold headline of healthcare fraud investigations compared to other types of fraud that affect the pharmaceutical industry. However, this type of fraud is equally as impactful to public safety and advancements in science and medicine. The DOJ recognizes the impact of research misconduct and is committed to focusing its enforcement activities on the area. Clinical trial sponsors can also minimize the research fraud impact by adding one or more of the elements mentioned to their existing compliance programs around clinical trial conduct.

There are five areas that a trial sponsor might consider including or updating within its current clinical programs to mitigate and address clinical trial fraud risk: prescreening potential investigators and trial sites, the inclusion

of specific legal terms to clinical trial agreements, directed training with an emphasis on research misconduct and whistleblower topics, auditing and monitoring efforts, and required reporting to health authorities. There can be no guarantee to mitigate all fraud or misconduct that might happen; however, developing and implementing a compliance framework specific to educating, identifying, investigating, and adjudicating instances of fraud increases the likelihood that the impact of physical and reputational risk, if it were to occur, could be minimized for the trial sponsor, the research conducted, and trial subjects.

Takeaways

- The Department of Justice (DOJ) recently announced increased enforcement of research misconduct/clinical trial fraud cases, which have dangerous consequences for the public.
- Research misconduct by clinical trial sites and investigators puts the public in harm's way and degrades clinical trial sponsors' data integrity and quality.
- Research misconduct can often also include Anti-Kickback Statute and False Claims Act implications.
- Implement a clinical trial fraud compliance program to mitigate risk covering five areas: investigator/site feasibility, clinical trial agreement terms, training, auditing/monitoring, and enforcement/reporting.

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3 U.S. Department of Justice, U.S. Attorney's Office for the Eastern District of Washington, "Richland Business Owner Sentenced to More Than 28 Years in Federal Prison for Falsifying Human Clinical Research Trials," news release, October 2, 2020, https://www.justice.gov/usao-edwa/pr/richland-business-owner-sentenced-more-28-years-federal-prison-falsifying-human.
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