
Fraud and Misconduct in Clinical Research

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Introduction

Fraud and misconduct in the research community occur more often than we would wish to believe. While it is impossible to provide a definitive figure for the frequency of its occurrence¹, surveys provide us with consistently (and perhaps surprisingly) high estimates. A meta-analysis² of such surveys showed that 2% of scientists admitted to having fabricated, falsified or modified data or results at least once, and up to 34% admitted other questionable research practices, such as plagiarism. Interestingly, the analysis showed that misconduct was reported more frequently by medical/pharmacological researchers than others. Considering that these surveys ask sensitive questions and have other limitations, the authors concluded that this is likely to be a conservative estimate of the true prevalence of scientific misconduct.

As if the frequency of fraudulent research was not concerning enough, the impact on affected individuals and the research community can be profound. At the very least, a single isolated case of fraud – say a clinical investigator fabricating a limited number of data points in a trial – will result in considerable costs to the pharmaceutical sponsor company and disciplinary consequences for the offending investigator. The costs to the company include additional resource for investigation and reporting of the fraud and possibly additional rework costs to repeat the fraudulent aspects of the research.

At worst, fraudulent clinical research affects the validity of data and impacts on the dignity³, rights, well-being and safety⁴ of research participants. Some cases have involved serious abuse of participants, most notably the Tuskegee Syphilis Study, American radiation experiments⁵ and the cases described in the Pappworth's seminal study⁶. It was cases of such gross misconduct that led to the development of Ethics Committees in many countries as well as the introduction of clinical trial legislation⁷.

Such ethical and other controls have nowadays made these extreme abuses a rarity, but clinical investigators who fraudulently include ineligible subjects into a clinical study still put the safety of these subjects at risk. Furthermore, widespread fabrication of data, if undetected, could result in the registration of a medicinal product based on unreliable data, thereby endangering the health of future patients.

Types of Fraud and Misconduct

There are a variety of definitions of fraud and scientific misconduct. Often, the terms 'fraud' and 'misconduct' are used interchangeably. Generally, fraud describes acts of omission and commission, consciously not revealing all data and consciously altering or fabricating data. Such falsification of data can occur at any stage of the research process, from initial design through to reporting results. Fraud does not include honest errors or differences in opinion and the usual definitions include an element of intent. Repeated non-compliance with the study protocol and GCP may be considered as an example of misconduct, although the end result may well be similar to deliberate fraud.

Wikipedia presents a useful and accessible definition from which a short summary has been provided below:

Fabrication is the publication of deliberately false or misleading research. This can be omission of critical data or results for example, the reporting of only positive outcomes and none of the adverse outcomes. Equally, statements can be made that are entirely unsubstantiated. Another form of fabrication is where references are included to give arguments the appearance of widespread acceptance, but are actually fake, and/or do not support the argument.

Plagiarism is the act of taking credit (or attempting to take credit) for the work of another. This is probably the most common type of scientific misconduct. Misconduct is not just aimed at those who do not list authorship, but also includes those who have not made substantial contributions to the research and claim it for their own. Suppression of significant findings is also considered a form of misconduct.

What is the Motivation for Fraud?

Human nature being what it is means that there will always be some individuals who are tempted into fraudulent behaviour – for a variety of reasons. Financial motivation is often perceived as the main motivation but a desire to progress one's career ('publish or die') can also be a strong motivator. Sometimes overwork plays a significant part. If an investigator has committed to conduct many studies with inadequate resources, falsification may offer a tempting solution to the dilemma. Conflicts of interest should not be ignored – consider the situation where a researcher has a significant direct financial or reputational investment in the success of a company's investigational product.

Once they have succumbed to temptation, fraudsters may continue despite the risks, hoping they can extricate themselves or thinking they will not be found out. Face-saving, personal vanity, self-importance or work pressures can all play a part in continuing the deception.

How are Fraud and Misconduct Detected?

There are broadly three ways in which fraudulent data or misconduct are detected: routine monitoring activities, data trending or mining and through whistle-blower reporting.

Monitoring

The clinical trial monitor is on the front line when it comes to the detection of clinical fraud. If given complete access to all documents generated during a subject's participation in a clinical study, the monitor is in a position to detect most types of fraud. Review of source data provides the opportunity to verify eligibility of trial subjects and the integrity of the data generated during the study. Cross-checking data from different sources such as the pharmacy, laboratory, radiology, etc., further enables the monitor to detect anomalies.

However, fraudsters will usually attempt to hide their activities so the monitor must be aware of 'red flags' that in themselves do not signify malpractice, but can be indicators that should initiate further investigation. Table 1 opposite lists a number of such 'red flags' and what they could possibly signify. It is important to note that all of the 'red flags' listed can and often do have simple explanations including ignorance of regulations and good practices, negligence or sloppiness. It is therefore important that monitors use their discretion when following up such indicators.



Table 1: Examples of ‘Red Flags’ and Possible Implications

| 'RED FLAG' | POSSIBLE IMPLICATIONS |
|--|---|
| <ul style="list-style-type: none"> ■ Alterations in source data, e.g. alteration in values that turn an ineligible subject into an eligible one ■ Use of masking fluid in source data ■ Obliterated or missing subject identifiers, e.g. on ECG printouts, scans, laboratory reports | <p>Altered or deleted data to hide ineligibility of trial subjects, or other non-compliance (can also indicate fabricated data for trial tests not actually performed).</p> |
| <ul style="list-style-type: none"> ■ Clinic note entries not in chronological order or entries apparently inserted between existing entries ■ Handwriting similarities between documents from different subjects, such as diaries or QOL questionnaires ■ Subject diary cards of CRFs appear 'too clean' and without errors ■ 'Too perfect' drug accountability records | <p>Fabricated data, e.g. trial assessments not actually performed, subjects not actually treated or even complete fabrication of data for subjects that do not exist.</p> |
| <ul style="list-style-type: none"> ■ Similarities between different subject signatures on consent forms | <p>Trial subjects have not provided their consent.</p> |
| <ul style="list-style-type: none"> ■ Monitoring visits frequently postponed by site staff ■ Site staff frequently absent during planned monitoring visits ■ Trial documentation not available for monitoring or long delays before documents are presented ■ Delays in completion of case report forms ■ Site staff are anxious, defensive or complaining about monitor's behaviour or attitude | <p>Behaviour that leads to obstruction of monitoring activity may indicate manipulation to avoid detection of fraudulent activity.</p> |
| <ul style="list-style-type: none"> ■ Investigator is obsessed with study payments | <p>Not significant in itself, but something to be aware of.</p> |
| <p>Unusual or unexpected data – often detectable without visiting the site itself, e.g.</p> <ul style="list-style-type: none"> ■ Unexpectedly low incidence of screen failures, adverse events ■ Repeated values or number preference in data where variability is expected ■ Data submitted at unusual times, on holidays or at weekends | <p>Fabricated data.</p> |

Data Trending or Mining

These terms refer to the use of data generated from the clinical trial to look for unusual trends or values that may be indicative of fraud. For these techniques to be effective, the study data must be available in real time. The increasing use of electronic data capture has made their routine application possible.

Statistically valid programmes are developed that take into account the expected variability of the data and then look for anomalous data trends, typically comparing data between sites. Patterns of data such as those described in the last row of Table 1 can be quickly identified and the site exhibiting the outlying data then selected for additional monitoring or directed audit activity.

Whistle-blowers

When a worker finds fraud or misconduct perpetrated by a colleague at the same institution and then reports it either to internal management or to an outside organisation, this is referred to as whistle-blowing. If there are inadequate controls to prevent and detect fraud within an organisation, whistle-blower activity may be the only way that it is revealed.

Investigations and 'Directed Audits'

Once there is suspicion of possible fraudulent research activity, the next step is to conduct an investigation. After reviewing the circumstances, one common approach is to conduct a specialised audit often referred to as a 'directed' or 'for cause' audit of the individual or organisation under suspicion. The process is similar to most quality audits but there are additional techniques and considerations in the preparation, conduct and reporting of a directed audit.

Preparation

Companies will choose their most experienced auditors to lead a directed audit as it is one of the most challenging audits to conduct and you usually only have one chance. Once a fraudster knows an investigation is under way, evidence may 'disappear'. As well as having expert knowledge of the relevant GxPs and regulatory requirements, the auditor must know their SOPs and processes, especially concerning fraud/misconduct and the conduct of directed audits. They must also have diplomacy, tact and persuasive skills, as well as highly developed interviewing and questioning skills. Routine auditing is aimed primarily at processes but when looking at fraud cases, the integrity of the individual is under scrutiny, meaning the auditor must always have the ability to remain calm and professional under pressure.

While some companies do not consider an audit plan is appropriate for a directed audit, so as not to restrict the investigation, a formal plan may help to define the scope and potential targets for the audit. For example, in an investigation of suspected fabrication of subject diary cards, a full review of the site investigator file (SIF) and drug accountability records may not be necessary and would waste valuable time on-site. However, some of these documents may be relevant – such as signature logs from the SIF and drug dispensing records to cross-check with subject visit dates and events. If an audit plan is written, it should allow for flexibility as the investigation may take an unexpected direction.

Directed audits require as much planning as time will allow, although time may be limited as these audits often need to be conducted urgently. Auditors should ensure they have a thorough knowledge of the protocol and relevant study documents, including monitoring visit reports which will need to be reviewed with even more care than usual. Discussions with study team members are essential to ensure good insight into the situation at site as well as what is typical and atypical for the study.

Finally, it is common practice to send at least two people to a directed audit which could be either as two auditors or an auditor plus an additional person such as an experienced study monitor. This is because, if during the audit, evidence of fraud is obtained, or false statements are made, it is important to have witness corroboration by two individuals.

Audit Conduct

Directed audits usually start with a series of preliminary interviews with site staff. The objective here is to establish a baseline understanding of the research practices at the site, particularly in relation to the areas under investigation. It is important that the auditors obtain clear and unambiguous descriptions of practice and procedures of the study and record these statements accurately, as they will be referred back to later in the audit. Having two auditors present during these interviews will ensure that the questions and responses are accurately recorded.

After the opening interviews, the auditors will review the documents related to the audit scope and target. It is not possible in a short article to detail the process of investigation, as each audit will take a different path, but there are some techniques that are common to all audits. The cross-checking of records from various sources is essential and auditors may ask for records that are not requested as part of routine monitoring. For example, if there are suspicions of subject visits being fabricated, in addition to requesting the subject clinic notes, the auditors may also request appointment books, department diaries, outpatient reception records and other records to check when subjects attended for study visits.

In conducting the audits, accurate documentation of the findings of the investigation is vital. The auditors' notes may eventually become evidence in a legal case, so every detail must be recorded. It is important to record only facts and not conjecture – for example, record what was said and not said, what documents are present, where there are conflicting facts and what information is missing.

If the auditors do find evidence of fraud, then it is common to secure this evidence by making copies of the documents – taking care to de-identify the document to protect subject confidentiality. The auditor should write on the back of the copy what the document is, where it was found and other relevant information.

Directed audits usually take more than one day to complete. Having more than one auditor present provides an opportunity to discuss with each other the progress of the audit in the evening and to plan the strategy for the next day.

If evidence is found that points towards fraud, it is important at some point during the audit to present this evidence to the suspected party. This process should not be confrontational or judgmental but taken as an opportunity for the suspected party to explain their actions. This is where the interviews conducted at the beginning of the audit have their greatest value. The auditor can refer back to these, for example "In our interview, Dr X, you stated that you did [xxx]. However, this document does not support this statement - please can you explain?"

Closing Meeting

The audit closing meeting is when the auditors present their findings. The ability to remain calm, professional and objective is vital at this stage. The auditors must communicate the facts of the investigation without criticism but openly and frankly. Even if there is clear evidence of fraud, the auditors will express this in a non-personal way. For example, rather than saying "You fraudulently entered ineligible subjects into this study" the auditor would say "I have evidence that subjects who were not eligible to enter the study had their clinical records altered to make it appear that they were eligible. These subjects were then entered into the study in violation of the protocol requirements".

The auditors will also explain what happens next, for example, that the information from the audit will be relayed to company management or the sponsor who will decide what further action is required.

Audit Reporting

It is usual practice for a verbal report to be made immediately following the audit so that senior company management and/or the sponsor are informed as soon as possible of the initial findings. The audit report should also be written as a priority once the audit is completed. The audit report should be factual and supported by summaries or transcripts of the interviews, together with any collected evidence. Company procedures should be followed and further investigations are usually required. If later it is found that the allegations are not substantiated, or are found to be untrue, there must be a process in place to clarify company records and restore any damage done to reputations⁸.

Communication and Reporting

Once directed audits and other investigations are completed, and a determination has been made regarding their outcome, it is essential that appropriate communication and reporting takes place in a timely fashion.

Internal Reporting

Having company SOPs to cover the detection, investigation and subsequent reporting of fraud is essential and all staff in the company should be trained on the SOPs or parts relevant to their role in the company. These procedures should include at least the following elements:

- Initial actions upon suspicion
- Escalation and communication procedures
- Confidentiality aspects
- Investigation requirements
- Evidence preservation
- Reporting responsibilities e.g. to regulatory authorities
- Whistle-blower protection

External Reporting

Many regulatory authorities require that sponsors of clinical trials promptly report to them their suspicions of fraudulent data^{9,10}, and Ethics Committees/Investigational Review Boards must also be informed.

When the FDA detects regulatory violations which are so significant and/or numerous that the scope, severity or pattern of the non-compliance supports findings and are repeated or willful and involve submission of false information to the FDA and or to the sponsor in any required report, the FDA will give the highest classification of action known as Official Action Indicated (OAI).

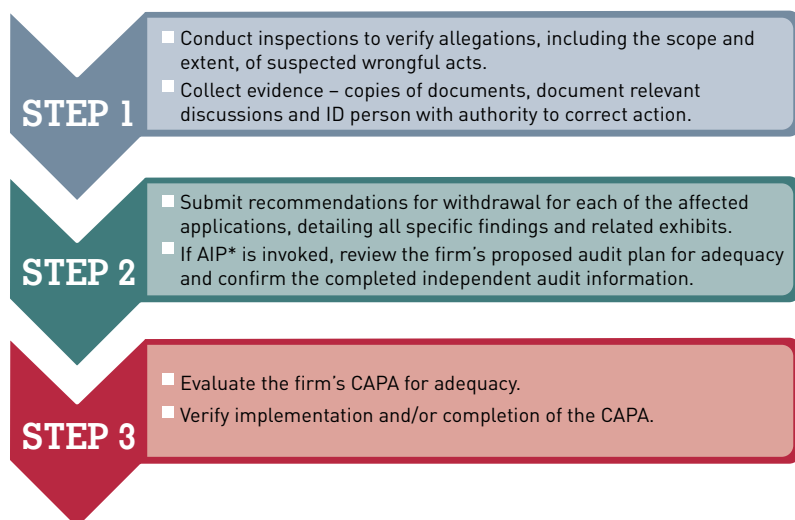
Figure 1 depicts the definition of what the FDA considers to be significant to be classified as an OAI inspection.

Figure 1: Inspection Outcomes Considered by FDA to be Designated OAI



The FDA process for following up on data integrity/scientific misconduct issues is illustrated in Figure 2.

Figure 2: Steps in FDA Investigation and Follow-up of Misconduct Issues



*Application Integrity Policy is a core part of the U.S. Food and Drug's policy, focusing on the integrity of data and information in applications submitted to FDA for review.



Prevention

Can we prevent fraud from ever happening? Probably not, but there are a number of well-recognised actions that every organisation should take to minimise the possibilities. In a 2008 'Nature' article entitled 'Repairing Research Integrity', Titus et al¹¹ listed six strategies to champion research integrity:

1. Adopt zero tolerance - all suspected misconduct must be reported and all allegations must be thoroughly and fairly investigated
2. Protect whistle-blowers - careful attention must be paid to the creation and dissemination of measures to protect whistle-blowers
3. Clarify how to report - establish clear policies, procedures and guidelines related to misconduct and responsible conduct
4. Train the mentors - researchers must be educated to pay more attention to how they work with their junior team members
5. Use alternative mechanisms - institutions need continuing mechanisms to review and evaluate the research and training environment of their institution, such as internal auditing of research records
6. Model ethical behaviour - institutions successfully stop cheating when they have leaders who communicate what is acceptable behaviour, develop fair and appropriate procedures for handling misconduct cases, develop and promote ethical behaviour and provide clear deterrents that are communicated.

Summary

If we consider the future for managing fraud and misconduct, we need to consider the driving forces. Fraud is usually conducted by intelligent people who must realise the consequences of their actions but have a naïve belief that they will not be caught or their attempts at fraud are too smart to be detected.

By having a thorough awareness of the implications of fraud, by instituting the practices described in this article and adopting the preventive measures recommended, fraud may never be eradicated but its impact can be minimised. Ultimately, we all have a responsibility and a duty of care to the people most damaged by this practice – to the patients we all serve in our daily work.



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The GCP Committee would like to evaluate if there is interest within membership to attend a seminar on Fraud and Misconduct in spring 2012. We have been conducting similar seminars periodically over the years and are now considering the development of a new updated seminar on this topic.

The seminar would be tailored to auditors working in the GCP environment in order to learn more about how to differentiate fraud and misconduct from non-compliance and how each can be managed. Topics of the seminar would include:

- An introduction to fraud, misconduct and non-compliance
- An overview of current regulations directed at fraud, misconduct and non-compliance
- A workshop exploring the differences in preparation and conduct of for-cause audits compared with routine site audits
- How reported non-compliances and suspected fraud can be effectively investigated during a site audit
- Interpersonal skills and interview techniques
- Conducting other types of directed audit e.g. investigation of critical systems failures



If you are interested, please send an email to: courses@barqa.com, citing the Fraud and Misconduct seminar in the topic line of the email.