

## Policy Change to Adequately Address Monitoring Conduct in a Risk-Based Environment

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### Abstract

In the new Risk-Based (RB) environment of clinical trials, policy to prevent and address misconduct and fraud by Clinical Research Associates (CRA) is virtually nonexistent. To date, misconduct of CRAs and its potential cost to patients and sponsors has not been studied, and thus, has not been addressed. Through strong policy change, it is time for regulators to voice a firm stance that misconduct and fraud will not be tolerated by any member of the scientific community.

Traditionally, onsite monitoring has been the standard for quality control with its emphasis placed on Clinical Research Site (CRS) conduct. Quality Assurance (QA) audits retrospectively sample CRS work-product for any possible mistakes or misconduct missed during the monitoring process. There are no regulated standards for how onsite monitoring visits are conducted, during which there is very little oversight of CRAs. Misconduct and fraud by CRAs is not well documented in the literature or in FDA guidance, and with the adoption of Risk-Based Monitoring (RBM) methods, there will be far less oversight of CRAs creating room for their potential misconduct and fraud. The resulting financial cost to sponsors, and risk to patient safety and rights, cannot yet be estimated. Regulators must make confronting CRA misconduct a priority.

### Notable Problems

Onsite monitoring has provided little evidence that quality of data is improved [1-5] and is an extremely costly part of clinical trial conduct. The first issue to be addressed by regulators is the need for standardization of monitoring processes and respective documentation. Since the management and documentation of monitoring visits is not specifically regulated, CRAs individually coordinate each visit according to company guidelines. The subsequent report generated by the CRA provides legal, written documentation of what occurred during the visit and any issues that were discovered. CIs and site staff are not privy to interim monitoring reports and must rely on a follow up letter (FUL) provided by the CRA. A review of documentation authored by 18 CRAs employed by two global Contract Research Organizations (CRO) was conducted which included 174 interim monitoring reports and available FULs, onsite evaluation of completed monitoring tasks, and investigation of reported issues. The preliminary analysis shows 14 CRAs (78%) falsified reports to document tasks completed during visits, such as review of informed consents, source document verification of data, and drug accountability; and/or fabricated issues related to CI oversight. Additionally, five CRAs (28%) consistently backdated entries in trip reports and/or FULs. More than 25% of FULs seeking corrective actions were not sent to CIs. Unfairly, unresolved issues could result in the issuance of a Form FDA 483 against uninformed CIs.

The second issue is CRA oversight while conducting monitoring visits [2]. Since CRAs have the freedom to organize the tasks of monitoring visits without oversight, there is a risk that key elements of a visit, such as informed consent and safety data review, are either completed carelessly, or negligently disregarded. This lack of oversight has resulted in fraudulent entries to monitoring reports as previously

described. Data review under RBM provides more liberty for misconduct to occur because these methods further the lack of CRA oversight, thus decreasing quality expectations of CRAs.

The third issue is accountability for misconduct and fraud in clinical research [3-9]. When searching the FDA website for guidance regarding misconduct and fraud committed by pharmaceutical industry staff, an abundance of descriptions and recommendations populate for CI misconduct. No information is supplied for monitoring misconduct or fraud. Since FDA guidance is heavily weighted toward CI misconduct and does not include the unethical behaviour of CRAs, new policy to address this disregard for regulations under the law must be provided to make accountability equitable for all.

### Cost of Misconduct

Currently, the cost of sponsoring a clinical trial is estimated to be greater than \$400 million [4]. It is not possible to estimate the cost to rescue a trial that has had enrolment difficulties, timeline breaches, or misconduct, but one can conclude that the additional cost would be an unnecessary financial strain to any sponsor company. The financial risk to pharmaceutical sponsors is increased with the lack of standardization of monitoring, CRA oversight, and CRA accountability for misconduct and fraud. Financial loss affects all of healthcare. Sponsor companies must support increased accountability of CRAs.

### Suggested Solutions

Clinical [1] research holds its own challenges, CRA misconduct being one. It is time to embrace the need for change and to extend the

application of consequences for misconduct to all members of clinical research. CRAs are an extension of the Principal Researcher developing the compound, biologic, or device. Just as the researcher would be held accountable for scientific misconduct or fraud, so should a CRA.

Solutions to the first and second issues bleed together. The development of a standardized framework for RBM, and its partnered onsite monitoring, must be penned and mandated by the FDA. Every “remote visit” should include patient rights and safety review being corroborated by regular third party compliance review of electronic audit trails triggered by CRA monitoring. Onsite visits should include the careful oversight of CRAs by CRS staff, including meeting minutes (MM) of any formal discussion between CIs, site staff, and CRAs. Review of MM should be a part of the onsite visit and CRAs required to sign them prior to the end of the visit. FULs should be provided to CIs at a minimum of two weeks prior to the subsequent visit and reviewed for accuracy against the MM; and if not received in that window of time, the visit should be rescheduled at the cost of the company providing monitoring services. Discrepancies between FULs and MM should immediately be addressed by site staff in writing to industry project management.

Third, audits conducted by QA should shift focus toward CRA conduct. RBM computer programs are designed to detect potential fraud at CRSs [5]. With changes to monitoring, QA must change. Focus on CRA conduct provides that change. QA initiatives should be completed by impartial, third party compliance consultant firms equipped to provide auditing and oversight, necessary root cause analysis for misconduct and fraud, and risk mitigation strategies as issues arise. These oversight activities should begin at the commencement of the trial [6-11].

Lastly, cost mitigation can be addressed during contract negotiations between the sponsor company and the agent(s) providing monitoring resources. Contracts should include financial liability of any contract CRA or CRO responsible for monitoring. Strategies have been adopted by sponsor companies to hold CROs financially responsible for contracted timelines and recruitment and retention efforts that were missed [6,12-17]. The same should hold for CRA misconduct.

## Conclusion

Clinical research conduct has transformed with the evolution of technology. The regulatory bodies of the US, European Union, and Japan have amended ICH/GCP E6 (R2) guidelines to meet the challenges of these changes. The revisions are based on cost savings and oversight of the use of new technological advances. One area that has consistently been overlooked is the conduct of unregulated, poorly managed CRAs who are the first line reviewers responsible for patient rights and safety and data integrity; they must be held accountable. With the advent of the new guidelines, now is the perfect time to address these conduct issues through policy change.

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