

Review Article

Qualitative features in clinical trials: coordinates for prevention of passive and active misconduct

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ABSTRACT

For many years, the quality concept in clinical trials has been discussed and recommended by Good Clinical Practice (GCP) guidelines. Regulatory Authorities and also the Public Involvement anticipate that the pharmaceutical industry will concentrate on creating quality frameworks amid the arranging and leading of conventions of controlled protocols. Nevertheless, many factors have been suggested as contributing to the occurrence of scientific misconduct within the research field, such as: personal and financial interests, site monitoring, available resources, workload, competition among investigators, and the implicit consent of sponsors. The negligence on data fraud represents not only omission but misconduct as well, in this case, a passive attitude intrinsically related to the act of transgression. A properly culture of research must be based on a fundamental ethos of integrity, openness and honest work of high quality in all parts of the research process. There is a need to change the focus from inspection-based quality improvement to planned systematic quality management within clinical trials. In search for a monitoring improvement, a full statistical way to deal with information recognition comprises of executing however many measurable tests as could be allowed on whatever number clinical information factors as could be expected under varied circumstances. Adoption of specific and preventive clinical trial monitoring procedures can identify potential misconduct and data fraud leading to improvement in overall data quality and scientific reports.

Keywords: Good clinical practice, Clinical trial, Data quality, Research misconduct, Fraud prevention

INTRODUCTION

Good clinical practice (GCP) guideline is the most accepted ethical and scientific standard for conducting clinical researches.¹ Despite the fact that the quality guidelines for Clinical Trials (CTs) have not changed throughout the years, consistence to these gauges has turned out to be all the more difficult to accomplish, because of the changing scene of the lead of CTs. In

science, the analytical process plays a central role. In fact, credibility of the quality evaluation process is one of the most valuable pillars on which the entire notion of “scientific quality” rests.

As simple as it may seem, along with ethical principles, the adherence to GCP parameters during the clinical trial (CT) process assures that the outcomes are credible and accurate, and also that the rights and integrity of the trial

subjects were properly respected.¹ Globally, committees for scientific integrity have been continuously discussing violations of scientific integrity. The problem is, however, that the decision whether or not scientific integrity has been violated in a particular case is entirely at the discretion of this board.

The main purpose of this comprehensive perspective (a semi-systematic narrative review of the literature) was to primarily describe the main features on the quality in CTs and its major challenges, in order to incorporate knowledge for further investigations based on a qualitative analysis of current evidence.

Is there a concept of quality in clinical trial?

As a result of the evidence-based medicine (EBM) approach, the GCP concept of quality has been systematically upgraded to include notions of benefit, for example, the “danger” of a New Medicinal Entity (NME). The Clinical Trials Transformation Initiative (CTTI) has described quality as: “the ability to effectively answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure, while assuring protection of human subjects”.²

According to the US Food and Drug Administration (FDA) Expectations of clinical trials and investigators (ECTI), the most deficiencies observed during site inspections include: inability to take after the investigational design and marked examiner proclamation/understanding; insufficient record keeping; deficient responsibility for the investigational item; lacking subject assurance, including educated assent issues; and Adverse Event (AE) recording and detailing deviations.³

Over the years, these have remained the areas of deficiencies at the investigator sites. However, Sub Investigators (Sub-I), Principal Investigator (PI), monitors, and sponsor play a significant role in the site performance. As reported by the FDA Medical Device Sponsor Inspection (MDSI), some of the common sponsor inadequacies were: unqualified monitors; failure to obtain signed investigator agreement; inadequate Investigational Product (IP) accountability; failure to notify FDA, investigators or Internal Review Boards (IRBs); failure to obtain FDA or IRB approval; failure to submit progress reports; and failure to secure investigator compliance.⁴

Regulatory authorities (RA), and also the patient and public involvement (PPI), expect the industry to focus on developing quality systems during the planning and conducting of CTs. Such systems depend on the development and implementation of standards for each CTs. The quality system requirements include: policies and procedures; quality assurance and auditing; personnel roles and responsibilities; corrective and preventive action (CAPA); and continuous training as well.⁵

The regulatory authorities’ worries about quality issues in CTs are convincing them to consider new ways to deal with evaluate the nature of these controlled studies. In this sense, the FDA is growing new methodologies of hazard-based investigation arranging, that would mean observation reviews of patrons and clinical examiners when the trial is continuous. Another major FDA initiative is the CTTI. The CTTI has applied several actions to identify practices that will increase the quality and efficiency of CT’s. The four priority areas for research are: design precepts, data quality and quantity (includes training and monitoring), study start-up, and adverse event reporting (AER). The CTTI has made worldwide suggestions to incorporate quality with the logical and operational strategy and in the conduction of CTs, simultaneously.⁶

Misconduct and fraud in clinical trials

Scientific misconduct/fraud is a violation of the standard codes of scholarly conduct and ethical behavior in scientific research. Fraud has been seen as an intentional deception made for personal gain or to intentionally damage another individual, falsifying and/or fabricating data, and misleading reporting of outcomes. According to the specialized literature, misconduct can be defined as: fabrication, falsification, plagiarism or deception in proposing, executing or reporting results of research, or deliberate, dangerous or negligent deviations from accepted practices in carrying out CTs.⁷ Notwithstanding, The Department of Health and Human Services (DHHS) establishes a more comprehensive misconduct definition (graphically presented in Figure 1).

The abovementioned transgression does not include honest error or genuine differences in the conception, carrying out, interpretation or comprehension in evaluating research methods or results, or misconduct unrelated to the research course. Within trials, mistakes happen and most are unintentional as they are provoked by misunderstanding or inattention to some minor element of the CT guideline. The effects of errors on CT results are not as significant since they are traceable and corrected once they are properly recognized.⁸

In certain cases of malpractice, data are falsified to align more closely with the researcher’s predicted results. As previously reported, data falsification could involve substituting one subject’s record for that of another subject, altering dates and results on subject records to fit protocol rules, altering the final score of tests, or claiming to have performed a procedure on a subject who, in fact, have never undergone that agenda.⁹ As a matter of fact, the most common types of misconduct reported in clinical research are: failure to follow an investigational plan and inadequate/inaccurate records.¹⁰

In more serious cases of scientific research misconduct, data may be completely fabricated (see some prominent examples in Table 1).¹¹⁻²⁶ In these circumstances, a

researcher might create records of interviews or subject visits that never occurred, insert falsified notes into medical records, or report progress data for a subject who had died.²⁷ Fabricating data involves creating entirely new records of evidence, whereas data falsification involves altering existing records.²⁸ Cases of intentional falsification and/or fabrication of research information

and misleading reporting of the results are less common than poor quality related to inefficiency, carelessness or professional recycling. The justifications for such unacceptable behavior can be financial, promotional, or contract retention. But probably more significant is the investigators' personal ambition.²⁹

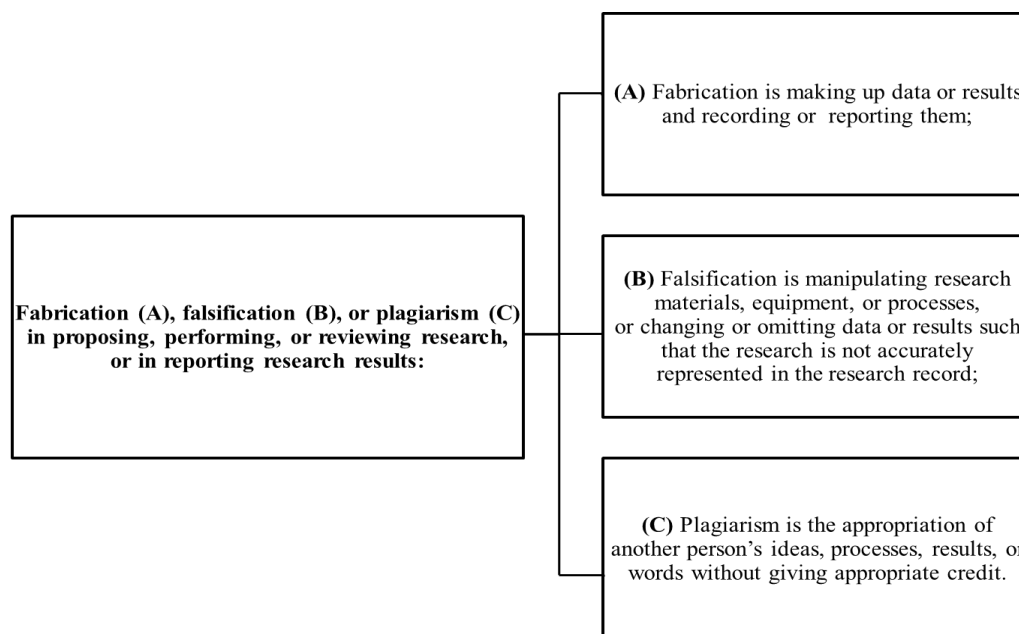


Figure 1: Department of health and human services (DHHS) definition of misconduct.

Table 1: Historic and contemporary examples on science fraud.

Scientist	Circumstance	Consequence	Main reference
Claudius Ptolemy	Reporting work by others as his own direct observations	Unknown	Newton ¹¹
Isaac Newton	Falsified data to make others agree to his theories	Unknown	Galton ¹²
Gregor Mendel	Selective reporting of results or even data falsification	Public disclaimer	Fisher ¹³
Roger Poisson	Falsification of eligibility data on multi-center breast cancer trials	Barred from research funding	Fisher, Weir ^{14,15}
Werner Bezwoda	Fabrication and falsification of data on breast cancer trials	Dismissed from position	Horton, Weiss ^{16,17}
Robert Fiddes	Fabrication and falsification of data and entering ineligible patients on a multi-center CT	15-months prison sentence	Eichenwald, Swaminathan ^{18,19}
Harry Snyder and Renee Peugeot	Falsification of data on CT's for a biotech firm	3-2.5 years prison sentence and financial restitution	Birch, Grant ^{20,21}
Yoshiaka Fujii	Fabrication of data on CT's in post-operative nausea and Vomiting	Dismissed from position along with the retraction of 183 articles	Kranke, Carlisle ^{22,23}
Anil Potti	Falsification of genomic data on cancer CT	Resigned position along with the retraction of 11 articles	Baggerly ²⁴
Hiroaki Matsubara	Fabrication and falsification of data on CT's of antihypertensive substance	Resigned position along with the retraction of 9 articles	Husten, Oranski ^{25,26}

The incidence of data adulteration

According to the literature, the reported incidence of misconduct in clinical trials is statistically irrelevant.³⁰ Apparently, the true proportion is difficult to estimate due to a composite of complex different reasons. As one might expect, in any attempt of estimation via survey of investigators, researchers who deliberately commit fraud are not liable to be anticipated about having defiled information. In addition, there are definitional problems. Is it just the barely characterized genuine instances of manufacture, misrepresentation or literary theft or something more extensive? Despite these difficulties, there have been various endeavors throughout the years to evaluate the pervasiveness or frequency of unfortunate behavior by means of overviews, reviews and different strategies, with clashing outcomes and conclusions.³¹

The negligence on data fraud represents not only omission but misconduct as well, in this case, a passive attitude intrinsically related to the act of transgression. In a meta-analytic paper composed of surveys of questionable research practices, roughly 2% of respondents admitted to information creation, misrepresentation or change and around 34% admitted to other "less genuine practices". Inquisitively, these rates bounced to 14 and 72%, individually, in reviews getting some information about the conduct of associates.³²

According to the office of research integrity (ORI) reports, there were more than 130 findings of scientific misconduct; 36 (26%) of these were in CTs or other clinical research.³³ Examples of those that ask about knowledge of misconduct, presumably by others, include a survey of members of the American Association for the Advancement of Science (AAAS) in which 27% of the scientists reported having encountered signs of misconduct; a survey of research coordinators in which 19% of respondents reported first-hand knowledge of misconduct – and that only 70% of these were reported; a study of Norway medical investigators in which 27% of

investigators knew of instances of fraud; a survey of members of the International Society of Clinical Biostatistics (ISCB), in which over 50% of respondents knew of fraudulent reports; a survey of British medical institutions in which more than 50% of respondents knew misconduct among institutional colleagues; and a survey of *New Scientist* readers, in which 92% knew of or suspected misconduct.³⁴⁻³⁹

The US ORI, the main head quarter charged of examinations of research on misconduct behaviours granted by sponsors, gives on-line outlines of the aftereffects of their investigations, including the "disciplines" for those found to have defrauded.⁴⁰ Uncommonly, there is even a blog (Retraction Watch) posting and talking about withdrawals of companion investigated logical papers, a large number of which are the aftereffect of scientific misconduct.⁴¹ More than 2000 scientific articles have been retracted over the last four decades. Almost a dozen of renowned authors have more than 20 retractions apiece. The quantity of withdrawals has expanded drastically as of late and the vast majority of these withdrawals are because clinical misconduct, particularly data fraud.⁴²

Can research malpractice be prevented?

Customarily, the arrangement of value confirmation has depended on reviews and investigation of the clinical trial sites (CTS) through standard operating procedures (SOP). This system has come under pressure because of the sum of several conflicting factors. A significant increase in the investigator site burden has been related to the number of unique study procedures and the rise in the average number of inclusion criteria, leading to an impact over the site performance.⁴³ A very comprehensive study has demonstrated the need of expanding definitions on the scientific misconduct practices beyond fabrication, falsification, and plagiarism and another one has offered a very modest but useful recommendation for fraud prevention (Table 2).^{44,45}

Table 2: A seven-step strategy for fraud prevention.

1) Oversample and add extra clinics	To enrol a larger sample than is needed and enrol a few extra clinics in the trial
2) Specify a maximum number of patients per investigator	e.g., no clinic site can contribute more than 5% of the total number of patients on the trial
3) Use of co-primary endpoints	e.g., when vulnerable end points such as diary data are used, culture data could be specified in addition to a patient diary
4) Solicited adverse event data collection	Under solicited adverse event collection, a clinic worker will question the patient at each visit on whether or not certain adverse events
5) Use of covariates in primary efficacy analysis	The statistical analysis plan should specify that the primary analysis is unstratified and without covariate adjustment;
6) Randomization policy	Avoid using trial-wide minimization methods;
7) Use of technology	Use technology that takes data from the patient and inserts them directly into the clinical trial database (e.g., statistical programs).

All research institutions are required to have internal control routines in order to carry out their activities in a responsible manner. The data inspectorate (DI) has passed advance audits prior to approval of processing of sensitive personal information in research projects to a locally nominated data protection inspector (DPI), for example, while they themselves now undertake a greater number of audits of ongoing projects. Many research institutions also have their own bodies and routines for monitoring the ethical and quality aspects of ongoing research projects.⁴⁶ Supervisors, as a rule, should be well acquainted with all aspects of a project, including quality control of data collection, electronic data processing and statistical analyses, in addition to contributing to the publication process itself.⁴⁷

The culture/routine of research must be based on an intrinsic ethos of uprightness and honest work of high quality in all parts of the research process, as well as awareness on the part of research institutions of their responsibility for the system (which includes different levels of representative/operative groups). In practice, the integrity of researchers themselves and internal social control are probably more significant than any kind of external control, which is chiefly designed to expose the most serious cases of fraud. Open communication in research groups about ongoing research projects, in addition to discussions on sound research practice, mandatory supervisory refresher training (continuous learning), and ethics accomplishment, should contribute to the promotion of well-grounded protocols and help prevent misconduct and fraud.⁴⁸

Different implementations of CT monitoring have been proposed in the literature.^{49,50} The most famous approach depends on "key hazard pointers", which are clinical information factors recognized as critical, and observed all through the trial against pre-determined thresholds.⁵¹ One site that surpasses the limit for a key hazard marker is hailed for promote investigation. For example, convention infringement could constitute a key hazard marker. Locales (and specialists) could be red-hailed in the event that they encountered convention infringement in more than, say, 10% of their example.

In search for a monitoring improvement, a full statistical approach to data observance comprises of executing whatever number factual tests as would be prudent on however many clinical information factors as could be expected under the circumstances: tests for extents, worldwide fluctuations, inside patient differences, occasion tallies, conveyances of absolute factors, extent of week days, anomalies, missing data, connections between different variables, and so forth.⁵² Thus, this simple algorithm could identify incorrect or unusual data for a trial subject or centers where the data considered together are too different to other sites.

The essential thought here is to contrast the information of each center and the information of every other site,

which requires no distributional presumptions and can along these lines be to a great extent automated.⁵³ Centers with outrageous information irregularity scores are deserving of further examination, with the point of clarifying the distinctions, retraining the site staff if required, or – in the most dire outcome imaginable – to reveal a misrepresentation that would some way or another stay undetected. Hence high data inconsistency scores are a statistical finding with no implied value judgment and should not be interpreted as a "data quality" index.

CONCLUSION

The approach to regulatory inspections seeking to ensure quality in CTs is similar to the known systems seen on production lines. Rejection of data after inspection is usually ineffective and often has no objective effect on the core of those mistakes. It is necessary to shift the focus from quality-based inspection to systematic management of planned quality. Potential methods of recommendations for educational (and, if necessary, punitive) measures should also be administered to prevent and guide researchers. More investigative studies and systematic analyzes are needed to clarify and guide all professionals involved in new pharmacological initiatives to achieve and follow the standard of care (SC) and the code of federal regulations (CFR) principles.

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