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Data Integrity in Global Clinical Trials: Discussions From Joint US Food and Drug Administration and UK Medicines and Healthcare Products Regulatory Agency Good Clinical Practice Workshop

Regulatory Considerations DMEG

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Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials. Regulatory agencies conduct GCP inspections to verify the integrity of data generated in clinical trials and to assure the protection of human research subjects, in addition to ensuring that clinical trials are conducted according to the applicable regulations. The first joint GCP workshop of the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) and the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA-UK) was held in October 2018 and provided the agencies' perspectives on the importance of data quality management practices on data integrity. Regulatory perspectives on data blinding to minimize introduction of bias, and the role of audit trails in assessing data integrity in global clinical trials were discussed. This paper summarizes considerations of both agencies on these topics, along with case examples.

Data integrity in clinical trials is a critical issue for the pharmaceutical industry and the research community alike. The consequences of not maintaining data integrity can be severe and include rejection of data for marketing applications, need to conduct additional studies, and reputational damage. There are also ethical issues around exposing research subjects to investigational drugs if the clinical trial is not managed in such a way as to ensure that the data can be used. Data integrity has always been fundamental to new drug development programs and to clinical research as a whole.¹ Clinical trial data generated forms the basis for regulatory decision making, and a key objective of Good Clinical Practice (GCP) inspections conducted as part of regulatory review is to reconstruct the study based on the data to confirm data integrity. Emerging technologies (such as mobile technology and telemedicine) and novel trial methodologies (such as adaptive designs, decentralized trials, pragmatic, and "real-world evidence" studies), alongside an increasing reliance on contracting and outsourcing of data services necessitate regulatory agencies to adopt modernized approaches to assessment of data integrity and to continually optimize these approaches in their review of data from global clinical trials. Despite these changes, regulatory oversight has remained consistently focused on the reliability of data generated and the safety of study subjects.

GUIDANCE AND STRATEGIES FOR ENHANCING DATA INTEGRITY

Recently, regulatory bodies have published guidance related to this topic.²⁻⁷ A common thread among these various documents is an emphasis on risk-based approach to data management, specifically targeting data and study procedures that are critical and have the greatest impact on maintaining subject safety and determining product efficacy. For example, the Medicines and Healthcare products Regulatory Agency (MHRA) Good Practices (GXP) Data Integrity Guidance and Definitions document discusses the data lifecycle, data governance, and other organizational culture features to be considered in a risk-based approach.² An open reporting culture in organizations should be encouraged as fundamental to data integrity promotion throughout the data lifecycle, including processes from generation or recording of data to destruction, if needed, and the intervening processes (Figure 1).

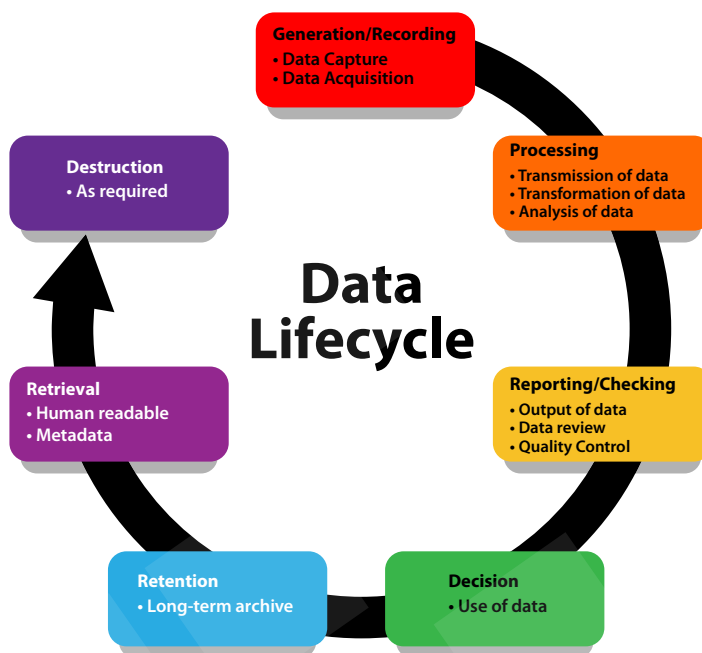


Figure 1. Data life cycle and its processes

It has been suggested, per the iceberg of ignorance study, that only a certain portion of problems are proximately known to senior leadership until communicated through several layers of an organizational structure.⁸ Data integrity issues will inevitably arise, and, therefore, strong leadership that encourages open reporting, investigation, and proportionate management of any failures is critical. Data governance—the arrangements to ensure that data, irrespective of the format in which they are generated, are recorded, processed, retained, and used—is essential to ensure the record throughout the data lifecycle and to guarantee the system is well-functioning. Data governance should address data ownership and accountability, evaluate how processes and systems are controlled and monitored, and assess the individuals involved in the system and their contributions, such as GCP training and the open reporting culture. When optimized, data governance should enable risks to be identified and minimized in an ongoing manner.

IMPORTANCE OF QUALITY AND RISK MANAGEMENT SYSTEMS

Clinical research is how therapeutic interventions are evaluated and this research is relied on by multiple stakeholders (e.g., pharmaceutical industry, regulators, medical personnel, patients, and caretakers) for making critical development, approval, and use decisions. To best inform decisions, clinical trials must be of high quality, address important questions utilizing study designs that are suited to the question being asked, and be well conducted so that study results will be credible. Despite the importance of data quality in clinical trials, until recently, quality measures within the clinical trial enterprise have been largely reactive rather than proactive. A shift toward more proactive quality and risk-based approaches has begun as stakeholders have looked to gain insights from other industries' experience in quality management and risk management systems that may be of benefit in the clinical trial arena. International Conference on Harmonization (ICH) E6(R2) also makes it clear that sponsors are expected to develop a quality management system using risk-based approaches to manage quality throughout all stages of the clinical trial process.⁹ The Clinical Trials Transformation Initiative Quality by Design initiative also promotes the importance of building quality into the scientific and operational design and conduct of clinical trials from the outset and provides a toolkit to assist stakeholders in implementing Quality by Design within their firms.¹⁰⁻¹²

Additionally, regulators have promoted the adoption of proactive quality and risk-based approaches in the design, conduct, and reporting of clinical trials through publications and guidance documents like the European Medicines Agency's (EMA) Reflection Paper on Risk Based Quality Management in Clinical Trials, the MHRA/Medical Research Council/Department of Health Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, and the US Food and Drug Administration's (FDA's) Guidance for Industry on Risk-Based Monitoring.¹³⁻¹⁵

GLOBALIZATION OF CLINICAL TRIALS AND INTERNATIONAL COLLABORATION

With the globalization of clinical trials, regulators have increasingly collaborated to optimize regulatory resources and oversight in the evaluation of the adequacy of clinical trial conduct. Since 2009, an EMA-FDA GCP collaboration has been ongoing and focuses on inspections for marketing applications.^{16,17} The Pharmaceuticals and Medical Devices Agency (PMDA) Japan has recently joined this collaboration.¹⁸ Additionally, a bilateral FDA-MHRA collaboration has been established that discusses GCP concerns across drug development programs. Information-sharing and collaborative inspections are key components of these collaborations, which are managed through confidentiality agreements between the agencies. Although there are commonalities in the inspection procedures and processes of the agencies involved, there are some differences that needed to be appreciated in order to forge these collaborations. For example, a key difference is that EMA inspections are focused on GCP systems and processes in clinical trials and also grade each finding and cite ICH E6 (R2) on GCP noncompliance.⁹ The FDA inspections, on the other hand, take an outcome-focused approach, focusing on data line listings to verify data provided in marketing applications and cite 21 Code of Federal Regulations (CFR).¹⁹ Additionally, the FDA has a unique group of GCP and bioavailability/bioequivalence reviewers who perform data reliability assessment based on inspectional findings from registration trials and convey the relevant findings to the assessors or reviewers in review divisions. These clinical trial inspections are generally conducted under the agency-wide Bioresearch Monitoring program by the Office of Regulatory Affairs field investigators. The FDA/Center for Drug Evaluation and Research (CDER) uses the Clinical Investigator Site Selection Tool as part of its risk-based approach to site selection.^{20,21} A summary of some of the common inspection features and

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Table 1 Types of GCP inspections – EMA, MHRA, and FDA

Regulatory body	EMA	MHRA	FDA
Inspectorate/ investigator cohort	Inspectors from EU member agencies	GCP Inspectorate	ORA/BIMO ^a investigators CDER GCP and BA/BE reviewers ^b
Data audits for marketing applications	Part of MAA for centralized products <ul style="list-style-type: none"> • Most clinical trials have been completed • Requested by the CHMP Basis for data audits – routine or triggered <ul style="list-style-type: none"> • <i>Routine</i> – No specific triggers identified during the MAA assessment. <ul style="list-style-type: none"> ◦ Inspection selection is based on various criteria (e.g., product type, therapeutic area, target population, location of sites, sites previously inspected by the FDA, etc.) • <i>Triggered</i> – Focus of inspection identified during the MAA assessment. <ul style="list-style-type: none"> ◦ Requested by assessors due to a concern about deviation from GCP in relation to the overall trial conduct or to the conduct at a particular site 	Part of EU MAA ^c Part of a national (UK) MAA	Inspections requested by CDER's review divisions in OND, OCP, and OGD <ul style="list-style-type: none"> • Sites (CI, sponsor, CROs, and monitors) selected from pivotal trials supporting marketing applications • Most routine data audit inspections are of clinical trials completed and submitted in support of an NDA, BLA, or ANDA • Risk-based site selection (using site selection tool) • BA/BE clinical and Bioanalytical sites (PK)
Routine surveil- lance inspections	N/A	National inspection programs – MHRA, like EU member states, conducts inspections for their individual territory Risk-based: systems or study-specific	IRB, RDRC BA/BE clinical and bioanalytical sites
Triggered, directed, or for- cause inspections	Performed by member states as part of national inspections, rather than EMA coordination, but can be done in collaboration across a number of member states if appropriate.	Triggered: systems or study-specific	Inspections based on referrals and reports of noncompliance about CIs, sponsors, CROs, and IRBs, and examine the inspected entity's conduct of trials Inspection assignments issued during any phase of ongoing trials, as applicable
Inspected entities	<ul style="list-style-type: none"> • Sponsors • CROs • Investigator sites • Laboratories • Phase I units • Bioequivalence facilities 	<ul style="list-style-type: none"> • Sponsors • CROs • Niche providers (e.g., vendors) • Investigator sites • Laboratories • Phase I units • Bioequivalence facilities • Noncommercial clinical trial units 	<ul style="list-style-type: none"> • Sponsors and sponsor-investigators • CROs • CI sites • BA/BE clinical and bioanalytical sites (PK) • Nonclinical (GLP) laboratories

ANDA, Abbreviated New Drug Application (for generic drugs); BA/BE, bioavailability/bioequivalence; BLA, Biologic Licensing Application; CDER, Center for Drug Evaluation and Research; CHMP, Committee for Human Medicinal Products; CI, clinical investigator; CRO, Contract Research Organizations; EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; GCP, good clinical practice; GLP, good laboratory practice; IRB, institutional review board; MAA, Marketing Authorization Application; MHRA, Medicines and Healthcare products Regulatory Agency; N/A, not applicable; NDA, New Drug Application; OCP, Office of Clinical Pharmacology; OGD, Office of Generic Drugs; OND, Office of New Drugs; ORA/BIMO, Bioresearch monitoring; PK, pharmacokinetic; RDRC, Radioactive Drug Research Committee.

^aFDA's Bioresearch monitoring program (BIMO) is an agency-wide inspection program with inspections conducted by Office of Regulatory Affairs/Office of BIMO Operations Investigators. ^bCDER OSI GCP reviewers periodically participate in inspections as subject matter experts; CDER OSIS BA/BE reviewers regularly participate in bioanalytical inspections. Systems inspections – Most MHRA inspections are part of MHRA's risk-based program and are systems-based focusing on the organization, and selecting some trials as examples. ^cPrior to September 2019.

distinctions across the agencies is provided in **Table 1**. International GCP collaboration has become one of the critical components for adequate regulatory oversight and assessment of data integrity given the (i) growing numbers of clinical trial sites per study and their locations outside the regulatory agencies' respective regions; (ii) finite resources, which limit the number of inspections that can be conducted; and (iii) accelerated product approval programs requiring high level of efficiency for marketing applications.

EFFECTIVE USE OF AUDIT TRAILS

Audit trails are an integral component of the electronic systems (eSystems) used in clinical trials for the capture of study data as they provide the ability to trace both data changes and system activity. Use of eSystems with well-designed and controlled audit trails can ensure GCP compliance and improve the quality of the system performance. Strategies for the effective use of eSystems with audit trails should be considered during the early stage of study planning (e.g., protocol design) to allow for the monitoring of the study and the investigation of any compliance issues. The design of the system audit trails should ensure that all data changes and system activities (eSystems contain logs that may store useful compliance information; e.g., changes to user access rights) are captured and that audit trails are not deactivated.⁹ Audit trails for data entry should have an automatic function to show what data element was changed, what the change was, who changed it, when and why it was changed,² and not obscure the original entry and any previous changes. Proper access controls will ensure that the changes are made only by authorized personnel. System audit trails should ensure the data changes are documented and that there is no deletion of entered data.⁹ Audit trails should also be considered for other parts of the clinical trial management system using a risk-based approach to accurate reporting, interpretation, and verification.⁹ In addition, it is important that audit trails can be easily accessed and reviewed during the study, as part of a dynamic system, and once the data are archived, which may be in a static format (e.g., flat pdf file). Consideration must be given to how these data can be restored to a usable format, if required. When data are archived, the audit trails should be retained in their entirety, with the ability to still link the audit trail with the relevant data elements. It is also very important to ensure that all the system audit trails are maintained to ensure they are available for future use. Finally, audit trails should not just be accessed during GCP inspections. Regular

review of audit trails during the study, using a risk-based approach, will help ensure data quality and allow for the early detection of any problems.²

Regulatory review of audit trails: Case examples

Example 1: During a sponsor inspection, inspectors reviewed the audit trails of the database that handled the primary efficacy end-point data. For half of the subjects in the pivotal study, the audit trail listed a single data originator, and all data entered on the same date. No explanation was provided. The sponsor later explained that when the contract research organization (CRO) transferred the primary efficacy end-point data from the first half of the study to a new database, the audit trails were not transferred. Therefore, the person conducting the transfer was listed as the data originator for the transferred data. The CRO was unable to recover the audit trails from the initial database. The sponsor was able to gather paper source documentation from the sites that allowed for primary efficacy end-point verification. However, multiple calculations were required to derive each primary efficacy data point from the paper source documents, requiring increased regulatory agency resources. In this case, if the source data for the primary efficacy end point had been electronic only, the reliability of the data for the first half of the study would have come into question.

Example 2: During a clinical investigator inspection for a pivotal, randomized, double-blind, pharmacokinetic (PK) study, review of the data listings in the clinical study report (CSR), as compared with source data, revealed that several study subjects seemed to have received opposite treatments (i.e., active drug instead of placebo), mixed treatments (i.e., active drug and placebo), or opposite dietary conditions (i.e., dosing under fed conditions instead of fasted conditions or vice versa) during the study. For instance, several subjects who received placebo had systemic drug concentrations, whereas other subjects on active drug treatment had no detectable drug concentrations. Moreover, several subjects who received active drug treatment with food were reported as having received the drug treatment under fasted conditions. The discrepancies seemed to affect multiple clinical sites that participated in the study. The agency consequently had significant concerns about the reliability of study data and communicated these concerns to the applicant. The applicant ascertained that, in lieu of the actual randomization schedule, they had inadvertently included in their submission the

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mock randomization schedule used by the Interactive Response Technology (IRT) vendor during the study design phase. Additionally, the applicant submitted study-specific and site-specific audit trails from the IRT covering the period of study design until study completion. Review of the audit trails verified that the correct treatment allocation and dosing under the correct dietary conditions occurred during the study.

STUDY BLIND

The intent of blinding is to mask the treatment assignment to prevent the introduction of bias in the conduct of trials and the interpretation of the study data. Blinding is particularly important in studies where assessments are subjective (e.g., pain or depression assessments). Blinding is also important in studies with objective assessments (e.g., laboratory tests) as individual subject or overall study management may be influenced by knowledge of the subject's treatment assignment. Furthermore, aggregate analyses by treatment group before database lock may potentially introduce bias into the ongoing management of the study.

Therefore, it is important even in open-label studies to mask the treatment allocation.^{22,23}

A schematic of data flow in a typical clinical study is presented in **Figure 2**. The solid arrows in the figure represent the most commonly observed data flow between systems, whereas dashed arrows represent the multiple potential pathways between systems that developers may choose from when integrating data systems. Regulators have observed incidents of premature data unblinding along most of the pathways illustrated. The arrows illustrate the critical points in a typical clinical study data flow where unblinding risks exist. There are multiple factors to consider in designing and executing a study to ensure that it is robustly blinded, including but not limited to the factors indicated in **Table 2**. Case examples illustrating how unblinding can occur in a clinical study and affect the integrity of the study data are summarized below. Unblinding case examples Characteristics, labeling, and shipping of the investigational medicinal product.

Clinical Data Flow Diagram

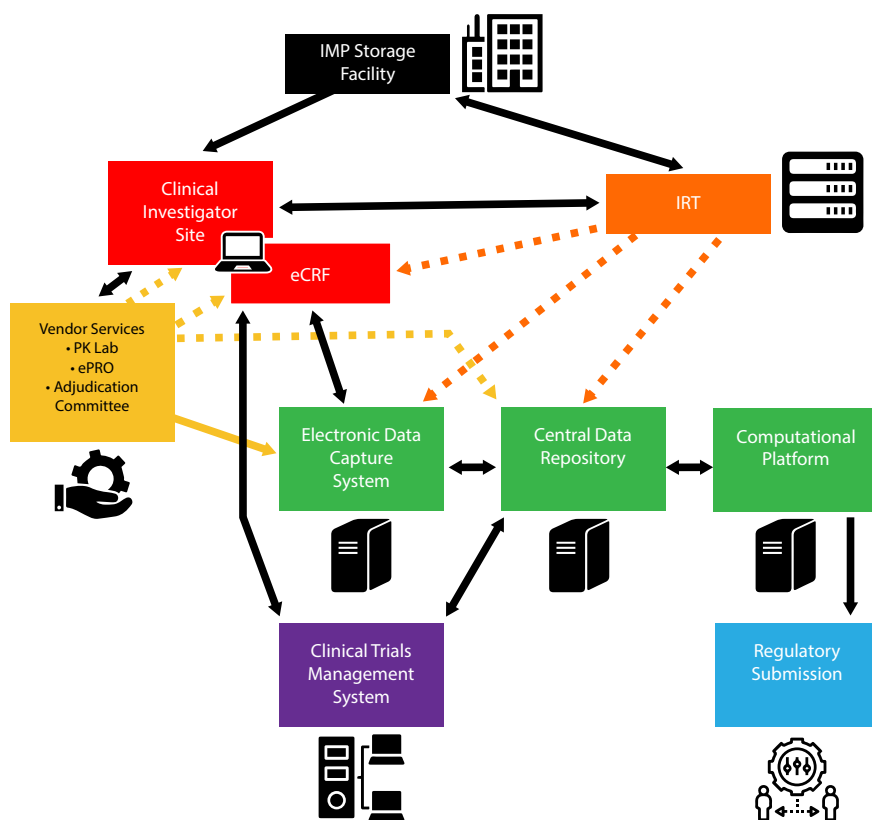


Figure 2. A schematic of data flow in a typical clinical study. eCRF, electronic case report form; ePRO, electronic patient-reported outcome; IMP, Investigational Medicinal Product; IRT, Interactive Response Technology; PK, pharmacokinetic.

Table 2 Factors to consider for ensuring a robustly blinded study

Topics	Factors to consider
Characteristics of the IMP	<ul style="list-style-type: none"> • Appearance of the IMP, active-controls, and placebos • Preparation of IMPs • Labelling of IMPs (batch numbers, lot numbers, and expiration dates) • Adverse reactions, including abnormal laboratory results, associated with IMP
Study processes, procedures, and practices	<ul style="list-style-type: none"> • Handling of randomization codes • Handling of PK data • Shipping procedures and documentation • Data collection, handling, and management procedures
Electronic systems used in the study	<ul style="list-style-type: none"> • Design specifications (eCRF and IRT system) according to the study protocol • Reports generated by the electronic systems • Access control (assigning and revoking user access roles and privileges to electronic systems) • Audit trails (design of audit trails, access to system, and review of audit trails)

eCRF, electronic case report form; IMP, Investigational Medical Product; IRT, Interactive Response Technology; PK, pharmacokinetic.

Example 1: Unblinding occurred in a double-blind crossover study where subjects received either Investigational Medicinal Product (IMP) or placebo during the crossover phases of the study. In this case, the IMP was a film-coated tablet and the placebo was formulated as green capsules filled with lactose. Because of the crossover design, subjects and study personnel could easily differentiate between IMP tablets and lactose-filled placebo capsules. In addition, because the primary efficacy end point was a patient-reported outcome assessment, unblinding very likely introduced bias when subjects answered the outcome assessment questionnaire. Blinding the appearance of IMP can become quite complex and expensive if a matching placebo is needed. If the expense and practicalities of creating a matching placebo or control are prohibitive, consideration should be given to alternative methods of masking treatment assignments to mitigate the risk of introducing bias into the study. When the risk mitigation strategy involves use of unblinded and blinded study personnel, care must be taken to ensure that study personnel with an unblinded study role (e.g., preparing and blinding the IMP) are not also assigned to perform blinded study activities (e.g., assessing primary efficacy end points or adverse events). It may also be possible to determine subjects' treatment assignments from batch numbers, lot numbers, expiration dates, and handling instructions that are listed on the products' labels. This may occur if study personnel have access to view information (e.g., batch number, lot number, expiration date, and handling instructions) found on the IMP kits or bottles provided to the site in conjunction with the IMP shipping documentation or manufacturer's certificate of analysis (COA). Adverse events associated with the IMP.

Example 2: Unblinding related to the IMP's associated adverse events occurred in a double-blind study

where one study arm experienced a higher incidence of dysgeusia than the other arm. It was possible to determine that dysgeusia was likely associated with the IMP by comparing kit, lot, and batch numbers from the COA, dispensing logs, and available PK data that was inadvertently shared with clinical sites. Although this information should be traceable (i.e., who received what and when can be reconstructed), sponsors should have appropriate controls in place to limit who receives this information. In particular, sponsors should avoid sharing preliminary PK data that could identify treatments with study personnel, except when necessary (e.g., medical emergency). Randomization documentation.

Example 3: Inspectors have also observed blinded study personnel with inappropriate access to randomization cards showing subjects' treatment assignments. In one study, these randomization cards were maintained in the Investigator Site File, which investigators routinely accessed. In another study, the assignment cards were stapled to the subjects' medical records, which were stored and easily accessible in the room where investigators were performing outcome assessments.

eSystems used in the study.

eSystems (e.g., IRTs, electronic data capture (EDC) systems, electronic Trial Master Files, and clinical trial management systems) may present risks to unblinding, and mitigating those risks necessitates understanding the system's intended use, its functionality, and the criticality of the data captured and maintained in the system, controlling the system design specifications (e.g., audit trails, access privileges, and eSystem reports), providing appropriate system oversight and management, and determining the root cause of any system error. If an error occurs, it is important to understand if it is isolated to the study-specific system build or if it is a system-level design error in which the same design error may occur across multiple unrelated studies.

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Example 4: Inspectors identified a poorly designed IRT reporting system that resulted in unblinding. The IRT produced blinded and unblinded reports, and whereas access controls for the two reports were assigned and restricted to either blinded or unblinded study personnel, as appropriate, both reports contained IMP lot numbers, which could be used to unblind the treatment assignment. A review of the system access logs also revealed that blinded study personnel had been able to access and view unblinded IRT reports.

Example 5: Unblinding occurred in a study where one treatment group received two IMP kits and the second treatment group received only one IMP kit. The IRT inventory report detailed the number of kits dispensed to subjects, which when accessed by study personnel unblinded them to the subject's treatment group. Furthermore, the impact on blinding was difficult to assess because although the system audit trail contained details of who viewed IRT reports, the audit trail did not capture which report was accessed and viewed. Thus, regulators concluded that all individuals who accessed the IRT reports viewed the inventory report and were unblinded to treatment assignment.

Example 6: Poor IRT management resulted in unblinding of several subjects in a double-blind, randomized study. In this study, the IMP supply was insufficient to match the recruitment rate for the study and the sponsor implemented a manual IRT supply process to transfer IMP from the slower recruiting sites to the faster recruiting sites. The manual process resulted in incorrect kits being shipped to sites. Hence, newly or previously enrolled subjects were not dosed because the available kits did not match the subject's treatment assignment. Furthermore, when site personnel used the IRT to assign a kit, the system alerted site personnel that all current kits were of the opposite treatment assignment for the subjects they were attempting to enroll or resupply. Therefore, when one subject's treatment assignment was unblinded at the site, many other subjects were also unblinded.

Example 7: Unblinding occurred in a large, double-blind, randomized cardiac outcomes study, where, appropriately, the IRT was programmed to permit emergency unblinding by the clinical investigator. However, global unblinding access privileges were granted inadvertently to over 100 clinical investigators and to multiple other study team members managing the day-to-day operations of the study. This example illustrates the importance of having appropriate eSystem access controls to prevent unintended unblinding.

Example 8: Inspectors have identified instances of unintentional unblinding related to poorly designed

electronic case report forms (eCRFs). Unblinding occurred in a study where eligible subjects were randomized to either a standard of care arm or an imaging arm. Although the clinical team was unblinded, the protocol required that assessors performing the end-point imaging assessments and scoring be blinded to treatment allocation. Regulators observed that the eCRF imaging pages used by blinded assessors to enter their assessments and scores displayed the treatment arm assignment of subjects in the headers on each page, resulting in all assessors being unblinded to the subjects' treatment assignments.

Data management practices

Example 9: Inspectors have regularly observed cases of inappropriate unblinding due to inadequate data management practices. In an open-label, randomized, active-controlled study, data were required to remain masked until after database lock to prevent the conduct of analyses by treatment group. Although the data management plan (DMP) specified that the firm's Data Management Group would mask data prior to transfer to the Statistical Group, masking procedures were inadequate and unblinded aggregate analyses were conducted and distributed to study team members on multiple occasions during an ongoing study. Requirements for data masking must be carefully considered to ensure adequate masking of all potentially unblinding datapoints, including data captured differentially between treatment arms, adverse events that are closely linked with specific products, abnormal laboratory results characteristic of specific products, and results of PK assessments.

Example 10: Unblinded safety reports for Data Monitoring Committees and suspected unexpected serious adverse reactions that require unblinding for regulatory reporting purposes may be an additional area of risk for unintentional unblinding.²⁴ Unblinding occurred at a CRO where unblinded and blinded 6-month IMP-specific safety line listing reports that covered several studies and many subjects were attached to an email and sent to the study email box for distribution to regulatory authorities and investigators. The unblinded report was inadvertently uploaded to a web-based online portal that was used as a communication tool for all study personnel (e.g., clinical investigators, study coordinators, and sponsor and CRO clinical research associates and study managers). Therefore, the unblinded report was widely available to all study personnel involved in the study. Fortunately, audit trails were adequate and useful in determining who had accessed the files, and the impact on unblinding could be properly assessed.

Third party eSystems

Study data are often processed and managed by individuals or organizations providing outsourced services, such as data management, adjudication, central electrocardiogram and laboratories, electronic patient-reported outcomes (ePRO), and electronic Clinical Outcome Assessment services. Study reports may be transferred through email, online portals, or clinical trial management system. There are also risks of premature unblinding as data flows to and from various third parties providing clinical trial services (e.g., central laboratory and various other testing services, central readers, and independent adjudication committees).

Example 11: Unblinding was noted to occur secondary to inadequate masking of treatment assignment on investigator site documentation transferred to a study's independent, blinded end-point adjudication committee. The clinical study site was required to send the source documentation that included the randomization assignment to a contractor to assemble the adjudication packages for the adjudication committee. Before transferring the information to the committee, contractor staff responsible for assembling the packages failed to recognize that source documents from the site revealed the treatment assignment. Inspectors noted that the contractor's procedures for masking and assembling blinded adjudication packages were incorrectly executed and the root cause of the unblinding incident.

Example 12: A contracted laboratory provided PK reports directly to the sponsor through email. The PK laboratory was unblinded before analysis so that only PK samples known to contain active IMP were analyzed. In such cases, laboratories will often provide the PK data to the sponsor in a blinded fashion so as not to reveal the treatment assignment. In this case, however, the laboratory reports included the sample analyses dates, which were missing for the placebo subjects, and this effectively unblinded 48 subjects. Further investigation revealed that the laboratory had study data transfer specification procedures that were not followed and that this same issue had previously occurred with three additional sponsors, which clearly indicated that the preventative measures implemented were insufficient. Handling of blinding codes in bioequivalence studies. Whereas typical bioequivalence (BE) evaluations are based on PK end points, clinical end-point-based BE studies are conducted in situations where a drug is not intended for systemic absorption, or measurement in the blood is not practical. Unlike open-label PKbased BE studies, clinical end-point-based BE studies are usually blinded

studies where IMPs are labeled with a randomization number or blinding code, which contain the drug products' identities. The sealed blinding code should be maintained at the testing facility to allow regulators to verify correct treatment assignment during inspection.²⁵

Example 13: In a BE inspection of a randomized, double-blind study, the IMP was labeled with a two-part tear-off label, containing the treatment identity underneath an obscured scratchoff text box. Upon IMP administration, one-half of the tear-off label was placed on the subject's dispensation record. Inspectors learned that the sponsor collected all original dosing records while the site retained copies only. During inspection, the sponsor sent the previously collected dosing records back to the site. However, inspectors noted that many subjects' records were missing and there were discrepancies among the treatment codes on the returned dosing records, the sponsor's data listings provided to the regulatory agency, and the study protocol. Thus, regulators could not confirm what product subjects received during the study. This example highlights the importance of proper handling of blinding codes. In summary, it is critical that sponsors, clinical investigators, and other study personnel understand the data flow, perform a risk assessment, and develop risk mitigation strategies in order to robustly maintain and protect the study blind throughout the conduct of the study and to ensure the reliability of the data. Moreover, GCP training for all study personnel that includes the importance of maintaining the blind, following the protocol-specific requirements and GCP documentation requirements, and maintaining and retaining study documentation is critical to mitigating the risks of unintentional unblinding. Sponsors should have robust control of the blinding procedures, appropriate handling of randomization codes and documentation that could unblind, and adequate standard operating procedures to ensure access to such information is restricted during the clinical study and before data lock. Likewise, it is important that regulators understand and evaluate the blinding and masking details and procedures implemented in the study to determine whether inappropriate intended or unintended unblinding of treatment allocation occurred during the conduct of the study. Inspectors may request a list of unblinding incidents on inspection and transparency with regulators is paramount when such events have occurred in the study. Early notification of such unblinding events is strongly recommended so that regulators have sufficient time to evaluate and consider the impact of unblinding events on the data, which may otherwise delay product approval. It is

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also recommended that sponsors and CROs regularly review inadvertent unblinding events across studies to identify opportunities for preventative actions for any recurring issues.

DATA MANAGEMENT

Adequate and robust data management procedures are critical to ensure the generation of high-quality and reliable study data.²⁶ Reliable data should comply with and meet protocol-specified parameters and be attributable, legible, contemporaneous, original, and accurate plus complete, consistent, enduring, and available (ALCOA plus standards).^{2,9,27} Discussed in this section are (i) important data management principles that should be incorporated into procedures and processes to ensure high-quality and reliable data and (ii) examples where poor or inappropriate data collection, handling, and management procedures affected data integrity.

Source data at the clinical investigator site

An important initial step for developing adequate and robust data management procedures is identifying and understanding the source data and its location(s). The protocol should identify if source data will be entered directly into the eCRFs or any other eSystems. The sponsor should ensure all procedures for processing source data exist at the clinical investigator site.⁹ Source data agreements should also be in place that define the location(s) of the source data required to support the protocol and case report form (CRF) data.⁹ All source data and associated metadata (e.g., audit trails) should be maintained and retained by the investigator, including data from ePROs, IRTs, electrocardiograms, and audio recordings, regardless of any sponsor-contracted third party. In circumstances when study data are directly transmitted from mobile technology (e.g., wearable and ePRO) to an online portal managed by a third party, investigators should have continuing access to and control of the study data, along with proper data management handling of masking, if applicable.

Data modifications

Sponsors and clinical investigators should ensure that all changes to the investigator's study data are documented and authorized by investigators or delegated study personnel at the site.^{9,28} Data queries that are raised should be resolved in the EDC system and captured in the audit trail, which should link the query text to the change made as a paper query form does. Any changes to study data entered into the EDC system should also be authorized by the investigator. Regulators have noted that, in some cases, sponsor

personnel have made changes to the study data without investigator authorization. For example, this has occurred when sponsors made corrections and other back-end changes to the database. Regulators recommend that a list of all data correction conventions be agreed upon by the investigator prior to study start-up to ensure that changes to their data are authorized by the investigator and that the investigator is made aware of all corrections before final sign-off of the CRFs. Final sign-off should occur before data lock. Sponsor personnel should not have open edit rights to the CRF/eCRFs.^{9,27-29} ICH E6(R2) describes a CRF as a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each study subject.⁹ All the protocol-required data collected should be managed the same as eCRF data. Therefore, investigators should oversee their data held by third parties and changes to data entered into any resulting databases (e.g., ePRO, electronic Clinical Outcome Assessment, IRT, and other site-generated data). Moreover, any changes to ePRO data should not require the sponsor's authorization, but should be supported by documentation in the subject's medical record that provides justification for the change. Of note, changes made to the ePRO data after the subject has spoken to the investigator should rarely occur and should be evaluated to ensure that bias has not been introduced. In addition, audit trails should be available to allow reconstruction of all changes to the study data.^{2,9,27-30} The sponsor may use the eCRF in workflows for data queries, coding, or extracting data for central monitoring. However, regulators have observed cases where the sponsor's medical monitor entered causality and expectedness assessments for adverse events and sponsor personnel and study monitors entered deviations into the eCRF data entry screens. As this is the investigator's data, sponsors should not be making edits in the eCRF without the investigator's authorization. In addition, investigators and delegated site personnel should be granted access to the eCRFs prior to the first subject visit. For access to the eCRF by site personnel, investigators should be involved in the oversight of account setup by the system administrator to ensure that only site personnel authorized by the investigator are granted access to the system. Because audit trails rely on username assignment, individuals should work only under their own username and password, or other access controls, and not share these with others.^{9,30}

The Paper Way

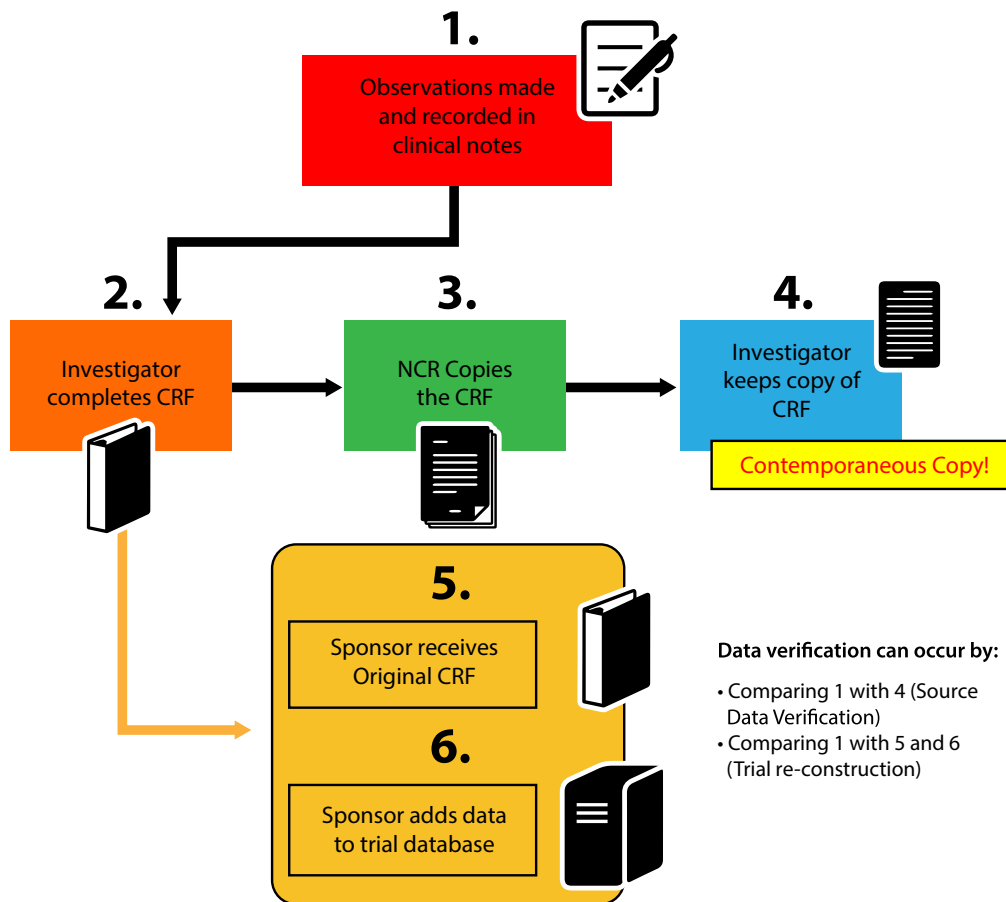


Figure 3. Data collection, query, and source data verification process using traditional paper-based CRFs. CRF, Case Report Form; NCR Copies, Non-Carbon Required Copies.

Clinical investigator control of their data

The investigator should control all source data, CRFs, and other site essential documents as the sponsor should not have exclusive control of the study data.⁹ Figures 3-5 illustrate the data collection, query, and source data verification (SDV) process when using traditional paper-based CRFs and eCRFs, and investigator control of study data (Figures 3-5). One solution to the data integrity risk of using eCRFs provided by the sponsor is to use a third party to host the data, which should be a separate legal entity and adequately independent of the sponsor. That is, they should not be a full-service CRO where clinical operations and other delegated study responsibilities are being undertaken for the study.²⁷ It is critical that audit trails be implemented and investigator access to the eCRF not be revoked prior to the investigator being provided a copy of the eCRF data and the corresponding

audit trails. The investigator should review the data, particularly when the investigator signs to indicate the data are complete and accurate. The use of a third party to prevent sponsor sole control would be undermined if the third party transfers the data to the sponsor for final distribution to investigators and the third party deletes the data. Data integrity can also be enhanced by implementing audit trail review, strict access controls, controls of processes for back-end changes, and encryption/checksum on any electronic copies of data. If the sponsor were to use their own data management system, implementing these controls, along with strict firewalls, would give regulators greater assurances of the integrity of the data. eSystems consistent with the final approved protocol Sponsors and investigators must comply with the final approved protocol,^{9,31,32} thus, it is critical that the CRF and other eSystems are consistent with the

Electronic Capture of Source Data

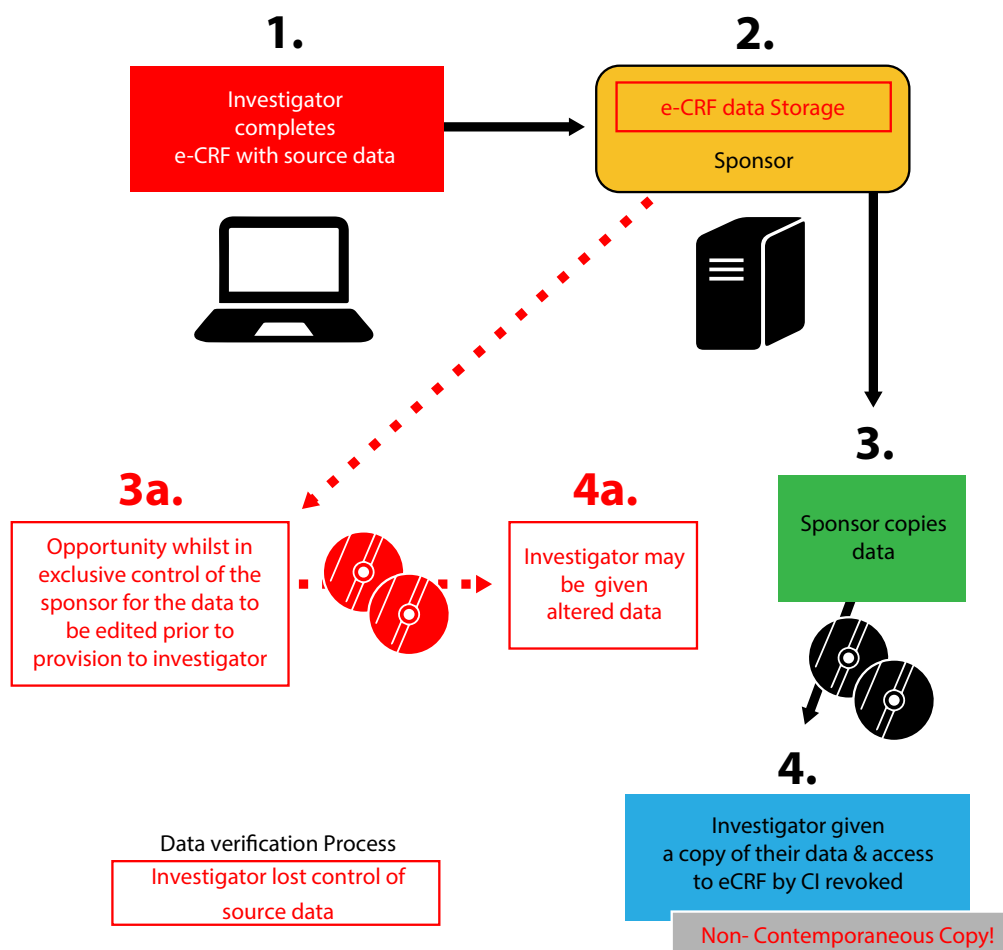


Figure 4. Electronic capture of source data. eCRF, electronic Case Report Form; CI, clinical investigator

protocol. A key issue often identified during inspections is that sponsors, CROs, and other third parties do not have adequate controls in place to ensure that the eSystems approved for release in the study (e.g., eCRF, ePRO, and IRT) are consistent with the currently approved protocol (initial or subsequently amended). Two scenarios may occur as a result: (i) sites use an eSystem designed for a protocol or an amendment that was never approved or (ii) sites are instructed to implement an approved protocol amendment; however, the eSystem design is inconsistent with the approved amendment and cannot be used.

eCRF with IRT integration

IRTs are often used for randomization, stratification, and IMP management. Investigators and site personnel enter clinical data (e.g., weight and baseline laboratory data) into the IRT to randomize subjects and calculate IMP doses, which is then transferred to the integrated eCRF. This allows the investigator to enter the data

only once. Because the IRT captures and collects study-related data, it is operating as a CRF.⁹ Thus, the IRT should be assessed against all GCP requirements for CRFs. Data integrity issues arise if the investigator changes eCRF data that has already been transferred to the IRT and the integration function has no mechanism to subsequently update the IRT data. When integrating data in the study database, electronic transfer methods should be used rather than any manual entry via CRFs. Electronic data transfer requires careful controls to ensure no data loss or alteration, the correct data are allocated to correct fields in the new environment, and the fields are compatible (e.g., data type, length, and formats). This requires detailed specification and validation testing. In cases where the sponsor manually transfers data from paper records (e.g., paper diaries), there should be a separate database that the sponsor uses to enter the data and the resultant data should be electronically transferred to the eCRF database.

Electronic Capture of Data using eVendor

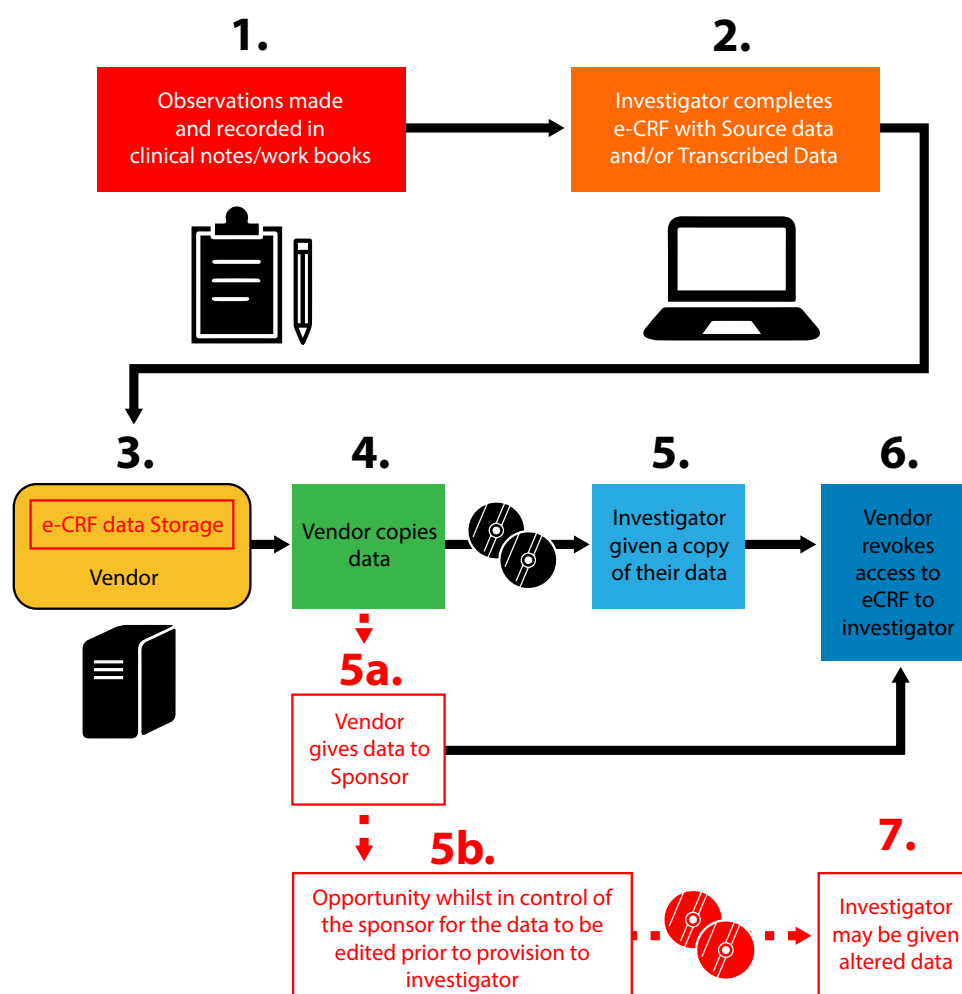


Figure 5. Electronic data capture using Vendor's eSystems. eVendor, vendor's electronic systems; eCRF, electronic Case Report Form.

eSystem validation

The sponsor may choose what validation model to follow; however, all validation documentation (for both the core software and the study-specific configuration) demonstrating that the eSystem is validated should be retained and available for inspection.⁹ Inspections of eSystem providers (e.g., IRT, ePRO, and eCRF) have revealed extensive documentation issues, which have led inspectors to question whether the documentation supported that the eSystem operated in the validated state. In one case, the documentation was so poor that regulators issued a critical finding because the vendor could not demonstrate that the eSystem operated in a validated state. For eCRFs, documentation is critical to show that all the necessary testing (e.g., data validation edit checks) has been completed. Furthermore, full documentation should be available for each release of the eCRF managed by change control processes. The protocol is the specification for the study and should

be used and referenced in all the documentation. Issues seen include eCRFs that are released on a draft specification, before validation, after the study started, or with incomplete validation. For example, in one study, edit checks were applied much later after release, after many subjects were recruited; therefore, the sponsor was not able to identify data entry and compliance issues and resolve them for future subjects in a timely manner. Programmed edit checks and ongoing enhancements intended to improve data at the point of entry should be as robust as possible from initiation and should be optimized if any issues or patterns emerge.

Contracts between eSystem providers and sponsors

Regulators have repeatedly observed contractual issues between sponsors and eSystem providers during inspections, some of which impacted data integrity. CROs and eSystem providers under European Union/UK regulation are required to comply with GCP

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and the approved protocol, which some contracts have not specified. Thus, the sponsor should be obliged to provide protocols and confirmation of protocol approvals to these contractors when requested. The contracts should include details on maintaining sponsor access to and management of essential documents and central records (e.g., software validation records) and retaining the data to ensure full dynamic data are available, as noted in a Q&A released by the EMA.³³

Database lock

Locking the database to prevent further changes to the data and declaring it fit for analysis is a key step and decision point in confirming data integrity. Before locking the database, a number of activities should be completed, including the resolution of all queries, importation of all external data, and finalization and reconciliation of all data. Good data management practices often recommend that data managers complete a checklist to document the completion (to include who, when, and where) of all actions as specified in each standard operating procedure (SOP).³⁴ Evidence of the action completed should also be available. Audit trails or system logs, generated by the database, should be available to confirm the date of the actual lock. The method of data extraction should be validated, and the resultant datasets stored in a secure location. Any unlocking of the database should be subject to strict control processes (for example, to prevent bias after unblinding of the data). For blinded studies, unblinding of the data should be after lock, statistical analysis plan finalization, and review of subject populations for analysis.³⁵ The investigator should verify and sign the CRF data used for regulatory submissions,⁹ even if the data are interim snapshots, and the electronic signature should invalidate if the eCRF data are subsequently amended as the study continues.

Protocol and GCP noncompliance

GCP requires that noncompliance be identified and rectified, including reporting serious breaches of noncompliance. Regulators expect that sponsors have a robust cross functional process to capture all noncompliance in a single central repository. The process should include a documented assessment of impact, a corrective and preventative action plan, and reporting of noncompliance to regulatory authorities, if needed.⁹ Documentation should be available to demonstrate use of all noncompliance data for impact assessment; for example, on dose escalation decisions, analysis populations, and Data Monitoring Committee meetings. Often, the review of the data and decision on analysis populations was not documented and, therefore, during inspection it

was not possible to reconstruct and confirm that it was done prior to unblinding the data. Noncompliance should be addressed in the CSR. The full list of all noncompliance should be available at the sponsor site because often the CSR consists of a subset of noncompliance using terminology such as "violation" or "important" or "serious."³⁶ How the subset was determined for regulatory submission should also be fully documented and explained.

Retention of data and documentation

All data management and statistical analysis-generated records and data should be maintained in the Trial Master Files and retained. The sponsor has flexibility in where these essential documents should be retained but the location for long-term retention should be defined in the quality system and should be appropriate to the type of file (i.e., dynamic file or flat file). The retention times required by regulation necessitates the need for managed archival of electronic files. The ability to view records and data in the eSystem active state is preferable, and this ability should be preserved during the time an inspection is most likely to occur (Figure 6). In general, the active database should be available during the live phase of the study and a locked database available during the reporting and regulatory submission phase. The dynamic nature of the files should be retained and available to be recommissioned to the active state (if the database has already been decommissioned). If it is not possible to preserve the dynamic nature of the file or eventually only flat files (e.g., pdfs) can be retained, perhaps virtualization or emulation of the system could be possible. Inspectors have observed during inspection that it was not possible to read the eCRF data on CDs/DVDs stored at the investigator site, or the data stored on the media was incomplete, particularly in terms of content and decipherability of audit trails. Furthermore, retaining these same discs, with flat pdf files, by the sponsor, has resulted in inspection delays when dynamic datasets were requested.

Data quality

GCP requires quality systems to be in place to ensure data reliability suitable for regulatory submission, decision making, or publication. Medicines given to patients can impact patient safety if data supporting efficacy and safety are not sufficiently reliable. Therefore, processes to prevent decision making on the unreliable data should be in place. Sponsors should focus their quality control efforts to minimize risks to the most critical study data and processes necessary to achieve study objectives.^{13,14} For example, critical data as driven by the statistical analysis plan

(e.g., study end points and protocol-required safety assessments) and processes (e.g., for evaluating, documenting, and reporting serious adverse events) should require a high level of quality control to confirm data quality. Data may be satisfactory without, for example, 100% SDV being completed for all data. Data validation activities should be focused on the data that are critical to study results based on the risk assessment. Any data cleaning process should include escalation measures if issues are identified. When risk-based (and statistically selected) source data review is performed, eCRF flag for SDV should corroborate and be reconciled with the monitoring plan requirements and SDV schema to ensure the planned statistical sample has undergone SDV.

Data management plan

It would be folly to attempt what has been presented without a DMP. Each study should have its own DMP, and it should be a living document, guided by the study-based risk assessment that establishes the data critical for reliability of results and subject safety, and should be dynamic throughout the life cycle of the study. It is not a stand-alone document but should be linked to SOPs in place governing its use and modifications.^{37,38} The SOPs should cover the setup, installation, and use of eSystems. The SOPs should also describe eSystem validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning.^{9,30,37} Writing the DMP should involve an expert, knowledgeable team that is familiar with the protocol and will ensure that the DMP will be carried out. Appropriate staff should be involved in the writing and review of the DMP as it is created, including those from clinical operations, statistics, and safety. There should be sufficient training in place for all involved, including investigator site, contract, and sponsor staff. There also should be responsive support staff always available for questions or issues/problems that arise during data handling. Every DMP should have a list of roles and responsibilities with contact information. Sponsors should describe in the DMP the electronic prompts, flags, and data quality checks that are designed to address, for example, data inconsistencies, missing data, and out of range entries.²⁹ The DMP should list data exempt from review (due to masking). The sponsor should also have a list of the individuals with authorized access to the eCRF in the DMP. The DMP should also address CRF design, data entry, data extraction, data validation, use of external data (such as off-site laboratory reports), quality

assurance and control, discrepancy management, generated reports, medical coding, reconciliation with the study safety database, data security, database locking and unlocking, data export, and data archiving. Regulators have seen several issues around poor data management planning, including inadequate CRF design, no plans for addressing the handling of missing data, not involving appropriate staff in planning and decision making, and not fully addressing issues that come up with external data loading and transfer. There should be quality assurance and quality control mechanisms at each stage of data handling. In addition, there should always be documentation of deviations from the DMP.

CONCLUSION

The first joint FDA and MHRA GCP workshop held in October 2018 reviewed fundamental and contemporary topics in data integrity and clinical data management. From these discussions, the importance of data integrity in clinical trials cannot be overstated. The FDA and MHRA discussions have shown that concerns with data reliability would have a negative impact on the acceptability of data submitted in support of a marketing application, or otherwise submitted for review by regulatory authorities. Importantly, data integrity issues can pose significant subject safety risks and impede our ability to ensure human subject protection in clinical trials. Concerns with audit trails, blinding, and data management overall have been presented as well as potential measures to prevent or mitigate the impact of the data integrity concerns. Data management procedures should be formulated to instill confidence that the data produced are reliable and of high quality. Efforts should be taken to ensure that audit trails are available and sufficiently robust to enable reconstruction of study events. Processes to maintain the study blind should be carefully designed and preserved throughout the study. In all cases, a careful risk assessment should be performed to identify the areas of criticality and this risk-based approach, in turn, can help guide appropriate allocation of resources for oversight of all data management processes and procedures. As part of data integrity oversight, there should be a mechanism to identify critical issues as they arise. Regulated entities should aim to communicate with regulatory agencies as early as possible after a significant issue is identified so that discussion can occur with regulatory agencies more expediently in order to cooperate on a strategy for addressing the data integrity issues adequately.

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MOVING FORWARD

International collaboration provides a pathway to enhance regulatory oversight to assure data integrity and the safety of subjects enrolled in clinical trials. Regulatory agencies will continue to look more closely at common GCP inspection findings, identifying similarities and differences to determine how regulators can work more efficiently to facilitate and coordinate GCP inspection efforts. The ability to share information among regulatory agencies bolsters the effectiveness of the regulatory authorities, and also aids in process improvement to better guide resource allocation for inspection coverage and align best practices. Through collaboration, regulatory agencies will find opportunities to provide guidance and regulatory convergence related to common GCP issues, novel trial designs and methodologies, and new technologies. Collectively, these developments help to strengthen the regulatory oversight capabilities of each participating agency and promote more efficient and effective review. Several emerging areas related to data integrity have been noted. These include sponsor oversight of eSystems and electronic health records used at sites, electronic source data, protocol deviations and management of these deviations, and novel clinical trial designs and the challenges in ensuring the quality and reliability of study data. The 2020 FDA and MHRA joint GCP workshop will delve into these issues. Additionally, international stakeholder collaborations, such as the ICH-E6 GCP renovation effort to accommodate emerging and evolving clinical trial designs and methodologies, and the GCP work group joint visit programs for technical harmonization under the Pharmaceutical Inspection Co-operation Scheme are currently underway.^{39,40} With continued collaborations, more efficient and effective conduct of global clinical trials is anticipated.

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