

GOOD PRACTICE GUIDE:

Validation and Compliance of Computerized GCP Systems and Data

Good eClinical Practice

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Validation and Compliance of Computerized GCP Systems and Data

Good eClinical Practice

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Preface

In September 2016, the website ClinicalTrials.gov [1] listed over 220,000 clinical trials in 191 countries. More than 180,000 of these trials were interventional studies investigating drugs or biological compounds, surgical procedures, devices, or behavioral aspects.

The global clinical study service market is currently estimated at approximately \$40 billion US (34.3 billion Euros) annually and is expected to grow up to \$64 billion US (54.9 billion Euros) by 2020 [2]. By that time, more than 70% of all clinical study services will be outsourced.

This overall growth, in combination with the increasing complexity of clinical studies, increasing cost pressures, and an increasingly patient-centric focus, requires a new model of virtually-integrated drug development.

The use of highly integrated computerized systems to collect, process, and analyze clinical data will also increase. These computerized systems will range from statistical programming platforms, data capture systems, and interactive response technology, to solutions for mobile applications, for electronic patient diaries and, in the near future, so-called wearables. These aspects pose a significant challenge with respect to oversight and control for sponsors and parties such as contract research organizations and technology providers.

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1 Introduction

In both the Good Manufacturing Practice (GMP) and the Good Laboratory Practice (GLP) world, principles of the validation of computerized systems are well known, and *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* [3] is established as industry best practice for these processes. The fundamentals of *ISPE GAMP® 5* [3] are based upon concepts developed within the pharmaceutical and biopharmaceutical manufacturing sector, but over time the key principles of the life cycle approach in this guideline have been expanded at a high level to be equally applicable across other functional areas, including Good Clinical Practice (GCP). The need to validate computerized systems used in the context of a clinical study has become a regulatory requirement as industry has moved from mainly paper-based processes to a large proportion of computerized processes.

ISPE GAMP® 5 [3] is a guideline for the validation of all GxP-regulated computerized systems and is accepted by the industry as well as by the regulators (the *ISPE GAMP® 5* is mentioned in the PIC/S Guidance on *Good Practices for Computerized Systems in Regulated “GXP” Environments* [4]) that the basic principles and concepts apply to computerized systems used in GMP, GLP, and GCP environments.

The aim of this eClinical Good Practice Guide is to highlight a common approach for application, as well as to discuss or address the differences in system validation practices between the GMP, GLP, and GCP environments.

This document is intended to adapt the general principles of *ISPE GAMP® 5* [3] to the field of GCP by addressing GCP (inter)national regulatory requirements. It provides a detailed interpretation of the GAMP validation concepts and enables a consistent and standardized application of the risk based validation approach and principles to processes and their supporting computerized systems within the GCP field.

Current International Council for Harmonisation (ICH) Guidelines include GMP and GCP requirements, with ICH E6(R2) [5] in particular addressing GCPs. Even though the guidelines are similar in many respects, there are significant differences in the level of detail and overall approach to computerized system validation. These differences have not been addressed adequately in regulatory or other guidances; thus, there is a need for clarification in this area. Specifically, the applicability of *ISPE GAMP® 5* [3] key concepts to GCP systems must be addressed.

Historically, GCP-relevant systems were very much limited to the pharmaceutical industry and their partners such as Contract Research Organizations (CROs). More recently, Information Technology (IT) systems in hospitals and investigator sites have been included in clinical study processes (e.g., via use of Electronic Data Capture (EDC) systems, delivering sub-systems such as Electronic Health Record (EHR) systems, or mobile medical devices and wearables for clinical use) and consequently are now becoming more and more GCP-relevant.

Every trial is a unique project that investigates a new product or medical aspect. Often the design of the trial and the procedures and processes associated with it are specific to the trial and lead to unique requirements with regard to the data to be collected by the investigators, and processed and analyzed by sponsors and/or CROs.

Both the project character of clinical studies and the very short overall timelines are a daily challenge for GCP quality organizations and require a flexible, scalable, and risk-based approach for ensuring the quality of processes, systems, and data.

In addition, the ownership of and responsibility for the data collected and processed within a clinical study need to be considered. For example, the investigator owns the source data, regardless of where it is stored, because it forms part of the subject case history. On the other hand, the sponsor is responsible for the accuracy, completeness, and consistency of the data collected and processed.

Furthermore, there are areas of overlap with the manufacturing field (e.g., in logistics for medicinal products) as well as with laboratory areas (e.g., when blood samples need to be analyzed as part of the trial).

1.1 Purpose

This Guide aims to provide guidance for all validation aspects related to computerized GCP systems including:

1. Understanding the business process supported by computerized systems
2. Understanding the unique risks related to clinical data
3. Understanding the complex issues of managing computerized systems on a variety of infrastructure platforms at different version levels across multiple organizations
4. Suggesting possible validation approaches, system classifications, and challenges
5. Ensuring compliance with applicable regulations with a special emphasis on data integrity and dataflows

First, the relevant processes and aspects related to a clinical study are presented, analyzed, and potential supporting systems identified. Then, possible validation approaches are outlined for these systems.

Considering the variability in clinical trials and organizational structures, the diversity to be found among computerized systems supporting clinical trials is significant. This document provides guidance by assuming that individual processes are supported by individual systems. If systems are combined (e.g., EDC and Clinical Trial Management Systems (CTMS)), the reader should consider all relevant aspects from the applicable sections of this Guide. Furthermore, all guidance given in *ISPE GAMP® 5* [3] for adequately scaling the validation efforts should be followed.

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2 Scope

GCP systems focus on the collection, storage, processing, compilation, transmission, and analysis of study data while ensuring the safety of the subjects.

Any GMP aspects with regard to manufacturing and quality control of investigational products are outside the scope of this Guide. This Guide will discuss all aspects specific to clinical studies, including, but not limited to, distribution to sites, randomization, and packaging and labeling in blinded trials.

Any GLP aspects with regard to the validation of analytical methods are not within the scope of this Guide; however, laboratories involved in the analysis of samples as part of a clinical study must be qualified, and any interfaces to laboratory systems (e.g., Laboratory Information Management System (LIMS)) must be validated.

The GMP and GLP processes and requirements excluded above are described in other documents and guidelines and will not be repeated here. Only processes and systems that have a direct relevance for the conduct of clinical studies are within the scope of this Guide.

Furthermore, there are numerous technical interfaces between various GCP systems, as well as interfaces to non-GCP systems. The technical aspects and the qualification of these interfaces are out of scope as other guidance documents exist; however, the key handover processes for clinical data that are often supported by interfaces are described in Chapter 4.

Ensuring ongoing data integrity in the context of the various life cycles is of paramount importance as the compiled study data is essential for the outcome of the clinical study. The specific challenges of integrated architectures utilizing interfaced validated computerized systems and the risks for data integrity are addressed in Chapter 7.

Typically, there are several life cycles that must be considered for computerized systems used in clinical studies.

For all systems, there is an underlying infrastructure life cycle covering the various elements that provide the platform for these systems. Additionally, a software development life cycle may be required to build custom software to address specific needs of one or more clinical studies. These are described in other documents and guidelines, which will not be revisited in this Guide. Only specific aspects that have a direct relevance for the conduct of clinical studies are within the scope of this Guide.

2.1 Similarities and Differences between GMP and GCP Systems

2.1.1 Product Quality versus Data Integrity

ISPE GAMP® 5 [3] states that “*Patient safety is affected by the integrity of critical records, data, and decisions, as well as those aspects affecting physical attributes of the product.*” Product quality in the GMP environment is defined as the quality of a manufactured physical product that is directly consumed by or used on subjects [6]. Product quality is therefore of paramount importance as people might be harmed by products of poor quality.

Companies manufacturing medicinal products address the quality requirements and regulatory controls through the implementation of a Quality Management System. This is an organizational structure with formally documented procedures, processes, and activities (e.g., extensive training) supported by processes for effective design, development, thorough testing and validation of computerized systems [6].

Ensuring the integrity of data managed by a computerized system is essential to support the evaluation of product quality and ultimately protect subject safety.

The result of a clinical study is not a physical product but rather data relating to the safety and efficacy of an Investigational Medicinal Product (IMP), which in this Guide includes medical devices, always under the premise that the IMP is of sufficient product quality. Or simply put: the end product of a clinical study is data.

The quality parameters that can be evaluated for a clinical study are correctness of the data and the integrity of data maintained throughout the study.

The importance of preserving data integrity in clinical research cannot be over emphasized. Regulatory agencies rely on the data to decide if products or procedures are safe and effective, and if they should be approved for use by patients. However, as data is collected, analyzed, processed, transformed, and corrected continuously, data integrity is at risk throughout the life time of the trial.

Since the data collected originate from study subjects, the protection of personal data and subject confidentiality provides additional challenges that are more predominant in the GCP field than in most GMP environments. For additional information related to data integrity, see Chapter 6.

2.1.2 Project Character of Trials

Every clinical study is conducted and managed as an independent project even if several studies use the same IMP. Each clinical study will be different since each either addresses different parts of the development life cycle (Phase I to IV or Non-Interventional Studies (NIS)) or varying product indications or endpoints.

Trial projects, especially across the various phases, vary greatly in terms of duration, number of subjects to be recruited, pace of enrollment, volume of data collected/evaluated, and expanse of geographic locations involved.

The life cycle of a particular study-specific system configuration, or in some cases the system itself, is primarily limited to the duration of the trial; whereas GMP systems are often in place for the life time of the manufactured product. While few pre-marketing trials run longer than three years, and even post-marketing trials typically do not run longer than five years, marketed products often exist for decades.

Even though GCP systems are frequently used for multiple studies, e.g., EDC system platforms, these systems must be adapted, configured, and sometimes deployed for each study separately to meet the trial-specific requirements.

2.1.3 Control over Technology, Process, and Training

In general, a validated computerized system is based on qualified infrastructure, validated software, qualified personnel, and well-defined processes. But for a number of GCP systems, some elements are only under limited control of the system owner and/or its users. Examples of these components include:

- EDCs
- Web portals
- Interactive Voice Response Systems/Interactive Web Response Systems (IVRS/IWRS) often referred to as Interactive Response Technology (IRT)
- Electronic Patient Reported Outcome (ePRO) systems

Often services and technology for clinical studies are outsourced to different service providers. For example, a sponsor may contract a CRO to conduct the trial and the CRO in turn uses a technology provider for an EDC solution.

The selection and ongoing control of the service/technology providers are critical. Systems used by numerous sites globally require robust support structures and a quality framework that can address the frequent changes to study setups without compromising quality or security. These aspects should be the main focus of vendor qualification activities.

Further information on vendor evaluation and control is included in *ISPE GAMP® 5, Appendix M2* [3].

It is recognized that the infrastructure and the personnel of the organization involved in conducting the trial (sponsor and/or CRO) can be as well controlled as within a GMP environment. But GCP systems are often accessed by hundreds or thousands of users at the clinical investigator sites involved in the trial, e.g., hospitals or general practitioner offices. These are typically outside of the sponsor organization, only bound by contracts and very often only participating in a few trials with the same sponsor; therefore, the operation, maintenance, and control of the system must consider the diverse infrastructure and the differences in organization, experience, and training.

The validation of GCP systems may need to address these aspects:

- The system users may be located in a large number of different companies or organizations in different countries and time zones
- The system users, who are distributed over several organizations, may follow different Standard Operating Procedures (SOPs), standards or policies, e.g., operating system patching, antivirus, browser versions, and policies for calibrating equipment
- The participating users may be restricted by local policies (e.g., IT security policies at hospitals)
- The local infrastructure may be very variable and complex (e.g., operating systems or browser)
- Changes in staff are not governed or controlled centrally

Consequently, not all elements of the computerized system are as strictly controlled as is typical in GMP systems. This severely influences the design of the system as it will need to:

- Be as independent from the local infrastructure as possible
- Use technical standards applicable across all sites
- Address local language and data requirements
- Address local and regional staff changes

As a key principle, the sponsor cannot completely delegate the responsibility for the conduct of clinical studies or the tools used in them, but must maintain adequate oversight. It is recommended to establish a control and/or governance body that is responsible for oversight of the clinical systems. The sponsor should chair this body. It should ensure that clinical trial systems remain in a validated state and that study-specific needs are adequately addressed.

2.1.4 Raw Data versus Source Data

In GMP systems, raw data is defined as any worksheets, (quality) records, memoranda, or notes that are the result of original observations, findings, measurements, or activities. Typically, the data has not been manipulated or processed by other means [7]. This data (or data derived from the raw data) is the basis for GMP-relevant decisions and activities. The raw data is not subject to interpretation and is collected in a tightly controlled process.

Source data in the GCP environment is “*All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.*” [5] Therefore, if source data is only electronic, specific regulatory requirements apply in addition to U.S. Food and Drug Administration (FDA) 21 CFR Part 11 [8].

The investigator is responsible for the completeness and accuracy of the source data as well as for the data entered into a system, and typically releases these data entries by signing the individual electronic Case Report Form (eCRF).

Documents containing any source data are part of the documentation of the trial and must be filed and archived.

For further information on eSource, see Section 6.5 Data Integrity in Computerized Systems Used in Clinical Trials: electronic Source Data (eSource Data).

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3 Regulatory Overview

3.1 History

In the late 1970s, information technology found its way into the clinical trial process and a fast-growing number of various types of computers were used to automate different trial aspects. To ensure the ongoing quality of the clinical trial process, which was well-defined when using paper, regulatory authorities started to establish rules and standard procedures to be followed when using such applications instead of the paper process. One of the most important aspects was the validation of GCP-critical systems used for clinical trials.

The FDA provided the first validation-related rules and guidance with the publication of a guidance document on the inspection of computerized systems in pharmaceutical processing, known as the “Blue Book” [54]. This guidance document, plus a series of Chapter 21 CFRs [11], were GMP- or GLP-related, and it was some time before the first regulations/guidance documents directly dealing with GCP were published.

In 1995, the World Health Organization (WHO) included validation and other system aspects as part of their Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products.

A key year was 1997. The ICH released their Harmonized Tripartite Guideline E6(R1) *Guideline for Good Clinical Practice* [13], which includes a number of system-related requirements (refer to Section 5.5 Process: Site/Partner Qualification for the details). This guideline was adopted by the three ICH regions and various other countries with or without modification.

In the same year, the FDA released 21 CFR Part 11 [8], which resulted in worldwide activities by all stakeholders participating in the clinical trial process (sponsors, CROs, and suppliers).

The ICH published one more guidance document dealing with *Statistical Principles for Clinical Trials* [14] in 1998 that included some high-level system-related requirements, which was adopted by the three ICH regions.

The FDA's *Guidance for Industry: Computerized Systems Used in Clinical Investigations* [15], released in 1998 and effective for nine years, provided a number of system-related requirements. Together with 21 CFR Part 11 [8], they were the main references used during system audits.

Two years later, the European Union issued its first GCP-related directive (Dir 2001/20/EC) [16]. This high-level document does not contain any system-related requirements, but refers to ICH GCP (E6(R1)) [13], and thereby strengthens the requirements listed in that guideline.

India released a set of system-related requirements in *Good Clinical Practice Guidelines* [17]. One more example is Tanzania, which issued a guidance containing system-related content in the same year. The NHREC *Guidelines of Ethics for Health Research in Tanzania*, revised in 2009 [18], is similar to 21 CFR Part 11 [8].

In the meantime, significant discussions ensued among the Health Care industry, supporting organizations like CROs, contractors and technical suppliers, and the FDA regarding the interpretation and implementation of 21 CFR Part 11 [8]. Concerns were raised that some interpretations of the Part 11 requirements would unnecessarily restrict the use of electronic technology in a manner inconsistent with FDA's stated intent in issuing the rule.

This could result in significant increases in the cost of compliance to an extent that was not contemplated at the time the rule was drafted, and discourage innovation and technological advances without providing any significant public health benefit. These concerns have been raised particularly in the areas of Part 11 requirements for validation, audit trails, record retention, record copying, and legacy systems.

As a result of these discussions the FDA reviewed the 21 CFR Part 11 [8] documents and related issues, particularly in light of the Agency's GMP initiative, and issued the *Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application* [9] in 2003. It is intended to avoid unnecessary resource expenditures in complying with Part 11 requirements. This 2003 guidance describes how the agency intends to exercise enforcement discretion with regard to certain requirements during the re-examination of Part 11 and offered a few options to simplify the process. Part 11 remains in effect during this re-examination period [8].

In 2005, Japan followed with a guideline for using electromagnetic records and electronic signatures [19] that is very similar to 21 CFR Part 11 [8]. This guidance document is supported by Japanese law and must be followed where applicable.

In the same year, the European Union published a second GCP-related directive (Commission Directive 2005/28/EC) [20]. This time, high-level system-related requirements were described and as before, it supported the requirements listed in ICH GCP (E6(R1)) [13].

The Pan-American Health Organization (PAHO) issued their guidance document *Good Clinical Practices: Document of the Americas* [21] in 2005, which was aligned with ICH E6(R1) [13]. Most countries in South and North America are members of this organization.

In 2006, South Africa released the *South African Good Clinical Practice Guidelines* [22], also aligned to ICH GCP (E6(R1)) [13]; and internationally, Clinical Data Interchange Standards Consortium (CDISC) provided the document: *Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials* [23].

One year later FDA's *Guidance for Industry: Computerized Systems Used in Clinical Investigations* [15] was replaced by a new version that contained slightly different content [24]. This guidance is still effective and has been referenced in newer documents as a validation requirement.

In the same year, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) released the *Good Practices for Computerised Systems in Regulated "GXP" Environments* [4].

This was adopted by the European Union one year later (2008) as a GCP Guidance – *Annex III to Guidance for the Conduct of Good Clinical Practice Inspections – Computer Systems* [25]. The guidance document refers to GMP Guidance – *Annex 11* [26], thereby indirectly connecting the GMP and the GCP worlds. European inspectors are using the PIC/S Guidance [4] when performing GCP system related inspections.

The FDA published in 2010 a draft *Guidance for Industry: Electronic Source Data in Clinical Investigations* [27], which was finalized in 2013. It promotes capturing source data in electronic form in an effort to streamline and modernize clinical investigations. Additionally, it is intended to eliminate unnecessary duplication of data and transcription errors as well as enable real time access to data for review.

In the same year, the European Union released a “Reflection paper on expectations for electronic source and data transcribed to electronic data collection tools in clinical trials” [28] dealing with the general principles for the use of electronic trial data handling and/or remote electronic data systems, system creation/modification, data creation/modification and transfer, as well as security and storage aspects.

With these two publications, EHR are mentioned by the FDA and the European Union for the first time.

Also in 2010, India issued the Central Drugs Standard Control Organization (CDSCO) *Guidance on Clinical Trial Inspection* [29] defining the items to be controlled during clinical trial inspections.

In 2011, South Korea released the first system requirements details in the *Regulation on Safety of Medicinal Products, etc. (Ordinance of the Prime Minister)* – Annex 4 *Good Clinical Practice* [30] and in 2012 the first system-related items appeared in African guidance documents by the release of the *Guidelines for Good Clinical Trial Practice in Zimbabwe 2012* [31].

The second revision of the EU GMP Guideline – *Annex 11: Computerised Systems* [26] was released in the same year containing detailed system-related requirements applicable also for GCP systems (*Annex III to Guidance for the Conduct of Good Clinical Practice Inspections – Computer Systems* [25]). Since then, Annex 11 [26] has often been cited as the European 21 CFR Part 11.

The *Guideline on Good Pharmacovigilance Practices (GVP): Module II – Pharmacovigilance System Master File* [32], published by the European Medicines Agency (EMA) in 2013, includes new legislation regarding the (potential) inclusion of system validation documentation in central files.

In the same year, Japan published the *Basic Principles on Electronic Submission of Study Data for New Drug Applications* [33] to provide the principal rules when clinical data is in electronic form. The rules cover the legal basis concerning electronic data management and notes for maintenance including electronic formats, version history management, signature, file name, etc. Examples of electronic documents are also provided. This document was replaced by a new revision one year later [34].

Also in 2013, EMA issued a “Reflection paper on the use of interactive response technologies (interactive voice/web response systems) in clinical trials, with particular emphasis on the handling of expiry dates” [35], which addresses the definition of standards for specification and validation of IRT systems (responsibilities of the provider, which can include in-house departments) including compliance to Annex 11 [26] as well as expected standards for quality systems.

Last, but not least, draft *Guidelines on Audio – Visual Recording of the Informed Consent Procedure* [36] was published by India that was required to be followed immediately [37]. The Guideline does not provide details about system requirements and standards for the audiovisual recording process, which may lead to confusion.

In 2014, the Society for Clinical Data Management (SCDM) released the white paper “eSource Implementation in Clinical Research: A Data Management Perspective” [38].

In 2015, the FDA released *Guidance for Institutional Review Boards, Investigators, and Sponsors: Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers* [39]. This draft guidance provides recommendations for clinical investigators, sponsors, and Institutional Review Boards (IRBs) on the use of electronic media and processes to obtain informed consent for FDA-regulated clinical investigations of medical products, including human drug and biological products, medical devices, and combinations thereof.

The ICH adopted an *Integrated Addendum E6(R2)* [5] at the end of 2016, which provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions [5]. The computerized system validation section provides more details than the original version from 1996 [13] but not to the extent of other regulations listed in this regulatory overview. ICH E6(R2) [5] is effective in Canada, the EU, and Switzerland; however, there is no information available for the US and Japan at this time. In the meantime, other countries (e.g., China) have followed with national laws/guidance, but generally these are more or less in sync with the requirements defined earlier by ICH, the United States (FDA) and the European Union (EMA).

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The latest (draft) guidance was published by the FDA at the end of June 2017: *Use of Electronic Records and Electronic Signatures in Clinical Investigations Under Part 11 – Questions and Answers* [40], which “clarifies, updates, and expands upon recommendations” in its 2003 guidance, *Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application* [9]. The draft guidance contains updated recommendations for applying and implementing 21 CFR Part 11 [8] requirements in the current environment of electronic systems used in clinical investigations, which now include cloud computing services, mobile devices and wearables. Once the final version is released, it will be an important cornerstone of clinical trial-related system validation requirements, clarifying some areas that are currently under discussion.

3.2 Regulations and Documents

Below is a list of the most important regulations and guidance documents:

- ICH Harmonized Guideline *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)* [5]
- Association of Clinical Data Management (ACDM): *Computer Systems Validation in Clinical Research – A Practical Guide and Validation and Management of e-clinical Systems in Collaborative Clinical Trials* (2015) [41]
- FDA *Guidance for Industry: Electronic Source Data in Clinical Investigations* (2013) [27]
- EU GMP Guideline – Annex 11: *Computerised Systems* (2011) [26]
- EMA “Reflection paper on expectations for electronic source and data transcribed to electronic data collection tools in clinical trials” (2010) [28]
- PIC/S *Good Practices for Computerised Systems in Regulated “GXP” Environments* (2007) [4], which was adopted by the EU one year later (2008) as Annex III to Guidance for the Conduct of Good Clinical Practice Inspections – Computer Systems [25]
- FDA *Guidance for Industry: Computerized Systems Used in Clinical Investigations* (2007) [24]
- Japan: Guideline for *using electromagnetic records, electronic signatures for application for approval or licensing of drugs* (2005) [19]
- Commission Directive 2005/28/EC of 8 April 2005 *laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products* (2005) [20]
- FDA *Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application* (2003) [9]
- FDA *Guidance for Industry: Computerized Systems Used in Clinical Investigations* (1999) (replaced and retired in 2003) [15]
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 *on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical studies on medicinal products for human use* (2001) [16]
- ICH E9: *Statistical Principles for Clinical Trials* (1998) [14]
- FDA 21 CFR Part 11 – *Electronic Records; Electronic Signatures* (1997) [8]

4 Process Overview

There are many regulations, guidelines, literature, websites, and seminars available that provide deeper insight into the regulatory background, organization, conduct, and analysis of clinical studies; therefore, we will only provide a short introduction here and highlight the aspects relevant to the validation of a computerized system.

Clinical studies are performed according to various (inter)national regulations to protect the participating study subjects as well as to ensure the development and manufacturing of high quality medicinal products according to the best standards. Those regulations cover all relevant aspects of study processes (e.g., sponsor, ethic committees, clinical investigators, central laboratories, manufacturing plants) as well as any supporting computerized system(s).

4.1 The Project Nature of Clinical Studies

The WHO defines “*a clinical study is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc.*” [42]

Clinical studies belong to one of the following phases:

4.1.1 Phase I (first in humans)

The medicinal product or intervention is tested for the first time in humans on a small group of healthy people (typically 20 to 80 volunteers) to evaluate the initial safety of the product or intervention. The main focus is on safety, e.g., safe dosage ranges, side effects etc.

4.1.2 Phase II

The medicinal product or intervention is tested on a larger group of subjects (typically up to 300 subjects) to determine the efficacy of the treatment as well as to evaluate further its safety. This is a critical step as the development of a new treatment often fails to demonstrate its efficacy or is shown to have toxic side effects that would prohibit further development.

4.1.3 Phase III

The medicinal product or intervention is tested on a large group of subjects (up to several thousand subjects) to determine its efficacy in comparison to a standard treatment. Phase III trials are the most expensive, time-consuming and difficult trials to design and run because of their size and comparatively long duration. These are typically the final trials done before regulatory submission and subsequent marketing. Also, Phase III studies are often conducted to test the efficacy of a treatment in additional indications or in combination with other medicinal products typically prescribed.

4.1.4 Phase IV

These are studies that conducted after the drug or treatment is marketed. The objective is to gather information on the drug's effect in various populations and on any side effects associated with long term use.

These definitions highlight that each clinical study is a project in itself. Every combination of indication, treatment, phase, and endpoint is possible; therefore, most systems supporting clinical studies must be highly adaptable to the needs of each trial. This obviously has an impact on the validation approach for such systems.

4.1.5 Non-interventional Studies

Other types of studies include, e.g., observational studies or epidemiological studies that are often conducted following established GCP standards, at least in part. These Non-Interventional Studies (NISs) as well as other types of clinical studies such as Investigator Initiated Trials (IITs) are within the scope of this document.

4.2 Stakeholders in Clinical Studies

In general, there are a number of major players in the conduct of a clinical study.

According to ICH E6(R2) [5], the sponsor is "*An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.*" Very often this is a pharmaceutical or biotechnology company, but may also be an investigator (in IITs).

Contract/Clinical Research Organizations (CROs) very often organize and manage trials on behalf of a sponsor. It should be noted that even if the sponsor has transferred all trial-related functions and duties to a CRO, the ultimate responsibility for the quality of the trial and for data integrity resides with the sponsor; thus, the accountability for the validation and maintenance of the systems in clinical studies is also with the sponsor.

Investigators who are qualified to conduct a clinical study cooperate with pharmaceutical or biotechnology companies as well as CROs. These investigators are physicians with access to the required subjects and are typically paid for their participation. The investigators are accountable for the safety of their subjects, for the integrity of the data collected at their site, and for the conduct of the study. They are responsible for ensuring that volunteers/subjects participating in the study understand the risks by establishing and documenting the informed consent process.

Clinical study subjects may be healthy volunteers or patients. The protection of the subjects' safety and wellbeing and the data obtained from the study are the aim of GCP and regulatory regulations.

Institutional Review Boards/Ethics Committees (IRBs/ECs) scrutinize the study for both medical safety and for the protection of the subjects involved in the trial. For clinical studies involving human subjects, approval by an IRB or EC is necessary.

Regulatory authorities approve clinical study applications and enforce adherence to the regulatory requirements throughout the trial to help ensure the safety of all marketed medicinal products and services.

Additionally, regulatory bodies, regulatory agencies, central and local ECs and IRBs review, approve, and oversee the clinical study. Approval and continuous review by these regulatory bodies must follow the international as well as the local regulations applicable for each country.

Other (non-CRO) service providers are parties/suppliers whose involvement depends on the type of study. These may include, for example, medical imaging services, laboratory services, pharmacies, manufacturing and packaging, and logistic services, EDC or IRT providers, and others. Either sponsors or CROs may contract them.

The relationships between all parties are managed by contracts and service level agreements.

4.3 Conducting a Clinical Study

On a very high level, a clinical study can be separated into the following parts (see Figure 4.1):

- Initiation and submission for approval
- Project management

- eCRF
- Site and partner/supplier Qualification
- Investigational product and its supply chain
- Subject recruitment
- Data entry and review (including monitoring)
- Adverse events reporting
- Mid-study changes
- Statistics
- Closure and submission
- Quality Assurance
- (Sample) Logistics
- Archiving

Chapter 5 gives an overview of these segments of a clinical study, including process descriptions, data and risks, validation approaches and challenges as well as the system classes typically associated with these processes.

4.4 Support through Computerized Systems

The above-mentioned processes are often supported by numerous computerized systems. To allow for a risk-based and efficient validation of the computerized systems, even in the context of individual trials, a layered approach has proven useful.

4.5 Validation Layer Model

To ensure compliance with the relevant regulations and guidance documents from ICH Good Clinical Practice (GCP), FDA, EMA, and other regulatory agencies (e.g., Ministry of Health, Labour and Welfare (MHLW) in Japan), as well as best practices dealing with the pharmaceutical industry (e.g., ISPE GAMP® 5 [3]), all GxP-relevant computerized systems used to support clinical studies (such as EDC, CTMS, IRT, EDMS, medical imaging, ePRO, eTMF systems and connecting interfaces) need to be looked at not only as individual applications but also as an integrated solution, often termed an “eClinical Platform.”

When working in an extensive environment with various systems to support different aspects of a clinical study from initiation to closure, it is helpful to separate the technical aspects into layers to simplify the validation efforts necessary to keep all technological components in a continuously qualified state.

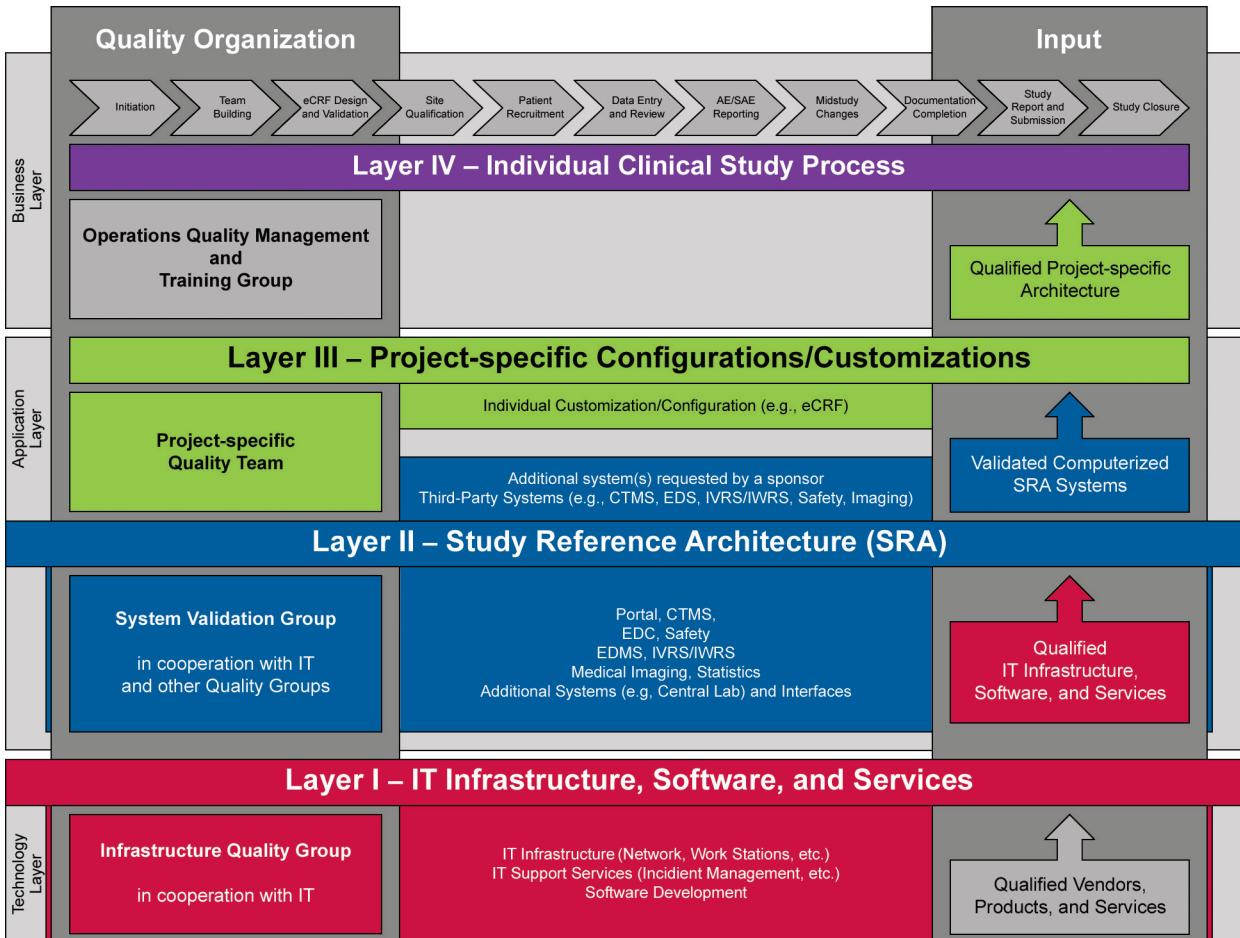
The Validation Layer Model shown in Figure 4.1 consists of four layers: three are system-related, the fourth is related to the clinical process.

- **Underlying IT Infrastructure** building the Technology Layer – Layer I
- **Study Reference Architecture (SRA)** part of the Application Layer – Layer II

- **Study Specific Architecture (SSA)** part of the Application Layer – Layer III
- **Individual Clinical Study Process** building the Business Layer, related to the clinical process – Layer IV

The Validation Layer Model covers all validation needs of the different components together with their connecting interfaces, and describes their roles and responsibilities within the framework.

Figure 4.1: Clinical Project Validation Layers – Overview



4.5.1 Layer I: IT Infrastructure

The IT infrastructure layer is the foundation of the eClinical Platform consisting of a subset of the overall corporate IT infrastructure, which might be extended by the infrastructure of qualified partners. IT infrastructure is the entire set of interconnected hardware, software, processes, and documentation supporting computerized systems and business services. Often these components are not dedicated to specific business processes or computer systems and may support the overall organization (e.g., servers, work stations, network, firewalls, routers, switches, communication lines, virtual private networks). The IT infrastructure (including shared platforms and generic architectures), which corresponds to the technology layer, needs to be in a continuously qualified state to provide a solid foundation for the activities performed in the validation Layers II and III.

The outcome of the Layer I activities are qualified shared platforms, infrastructures, architectures, suppliers, software products and services. For more information and guidance on infrastructure, see the *ISPE GAMP® Good Practice Guide: IT Infrastructure Control and Compliance (Second Edition)* [43].

4.5.2 Layer II: Study Reference Architecture (SRA)

The SRA is a composition of various in-house and third party computerized systems with connecting interfaces that are maintained as default architecture to provide clinical study-related services, e.g., an EDC platform system, a CTMS, an IRT system, or a safety system. Included in this layer are all standardized interfaces that do not require trial-specific configuration or customization.

These core systems, all following their individual system life cycles according to *ISPE GAMP® 5* [3], are kept in a validated state throughout their life cycle. The scope and type of validation depends on the specific GxP risk associated with the system and business process.

Together with the trial-specific configurations and/or customizations, which are described in Layer III, the eClinical Platform is part of the application layer.

Outcomes of Layer II are validated computerized systems building the SRA, connected by qualified interfaces.

4.5.3 Layer III: Study Specific Architecture (SSA)

Layer III deals with the development and validation of individual clinical study applications. This includes extensive study specific configurations and customizations, e.g., building eCRFs and ePRO as well as IRT deployment. All of these activities are driven by requirements based on the study protocol. The SSA includes the integration and validation of additional systems/interfaces if necessary due to trial-specific needs, e.g., an interface between the EDC (at the technology service provider) and the safety system (at the sponsor).

They are based on the SRA. Mid-study changes based on alterations of the study protocol often impact only the SSA. For example, changes to the eCRF typically do not require modification to the underlying EDC system.

During development and validation, individual sponsor requirements resulting from the type of study and/or special conditions are considered on top of the generic SRA validation requirements. Associated risk assessment efforts are focused on areas where subject safety and data integrity are at risk. This applies across the life cycle of a system from conception to retirement, which means that later mid-study changes may require additional risk assessment activities.

The Layer III outcome is a validated, clinical project-specific architecture that supports an individual study project.

4.5.4 Layer IV: Individual Clinical Study Process

Layer IV is a business layer that is not directly system-related; however, trial-specific operational aspects with regards to documentation (e.g., of source data verification, access, or data reviews), process descriptions (in SOPs, work instructions, etc.) and training (training materials and training documentation) are covered in this layer. This layer is necessary to maintain regulatory compliance for clinical study processes supported by computerized systems.

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5 Process Model

5.1 Process: Study Protocol and Submission for Approval

5.1.1 Short Process Description

The planning and initiation of a clinical study is the responsibility of the sponsor. Several internal and external parties are involved in the planning process; thus, cooperation and coordination are vital.

Once the decision has been made to conduct a clinical study, documents required for the submission of the application to the respective authorities and (institutional) ethics committees are created. The central document is the study protocol (subject to possible later amendments).

The sponsor of the study is responsible for developing the study protocol. This document is a description of the clinical study. A carefully designed protocol is not only critical to outline the research questions and ensure that the correct data is collected, but also to guarantee subject safety. The study protocol describes the scientific rationale and objectives of the trial including a risk-benefit analysis, the trial design, subject population, research procedures and methods, investigational product characteristics and dosage. Even though competent authorities and ethics committees review the study protocol and all other important documents prior to the start of the study, the overall accountability for the rights, safety, and well-being of the participants remains with the sponsor.

Each study will have at least one principal investigator who is usually involved in the discussion and development of the study procedures. Furthermore, the sponsor is required to qualify all involved parties (stakeholders), especially the investigators (see also Section 5.5).

Only after all required documents are approved by the principal investigator, all relevant authorities, and the ethics committees can the study be conducted in the territory for which the approval is valid.

As defined in the protocol, the data collected during the conduct of the study will be recorded in the Case Report Form (CRF) (see ICH E6(R2) [5]), which may be either paper or electronic (eCRF). All relevant study documents, including correspondence, are filed in the Trial Master File (TMF), maintained by the sponsor, and/or in the Investigator Site File (ISF), maintained at the study site. The TMF/ISF can be preserved as paper or electronic files (see also Section 5.12).

5.1.2 Data and Risks Associated with Process

Key documents created and collected in this process are:

- Study Protocol (including data management, statistical analysis, safety processes, etc.)
- Monitoring Plan
- Data Management Plan
- Statistical Analysis Plan
- Approvals by Principal Investigator(s), IRB/EC, and Health Authorities

In terms of risk, the documents compiled during the initiation phase do not contain any subject data; therefore, the direct risk is low for the study subjects. However, the study protocol is of fundamental importance to the conduct of the study, hence the associated overall risk is medium.

All study-related documents may be maintained in a Clinical Trial Management System (CTMS) or Document Management System (DMS) (see Section 5.12). Control over the approval status and changes to the documents during the conduct of the study are essential to preserve regulatory compliance. The risk associated to these documents is medium.

Another item to be determined in this phase is the number of study subjects, n, also called overall Enrollment Target or Sample Size. This number carries medium risk. If it is too low, then the study subjects have been exposed to the risk of a clinical study without scientific benefit because the results are not statistically significant. If this number is higher than necessary, then more study subjects than needed are exposed to the risk of a clinical study.

5.1.3 Validation Approach and Challenges

The CTMS or DMS involved in the process of a study initiation must be validated with a focus on:

- Tracking functions for all documents to ensure that compliance can be monitored
- Availability of relevant data for audits and inspections
- Electronic/digital signatures, if applicable

Typically, the process for study initiation and study conduct is standardized and does not require major adaptations from one study to the next.

Often, specialized statistical software is used to determine of the number of study subjects needed.

5.1.4 Typical Associated System Classes

There are a number of Commercial Off-The-Shelf (COTS) CTMS, DMS, or clinical study-specialized DMS like eTMFs available, but pharmaceutical companies and CROs often have custom-built systems as well.

COTS CTMS and DMS are typically classified as GAMP Category 4, while the custom-built software is classified as GAMP Category 5. The validation of these systems for their intended use should be sufficient for almost all studies. In summary, the majority of the validation activities are located in Layer II of the Validation Layer Model.

The specialized statistical software used to determine the number of study subjects can vary from using functions as standard, which means GAMP Category 3 (comparable to COTS) over configurations, which is GAMP Category 4, to custom code, which is GAMP Category 5.

5.2 Process: Project and Clinical Study Management

In this Guide, the process Project and Clinical Study Management is divided into two sub-processes: Clinical Study Management and Project Management, with their respective descriptions and validation approaches. Although there is a general trend towards merging these, it is reasonable to consider each process and their respective systems separately.

There are multi-tool off-the-shelf CTMSs available that support the trial management process from beginning to end. The CTMS can be connected to various other software products used during the conduct of the trial, such as EDC systems, financial systems, and logistics systems. Today, much of the data used for project control is often maintained outside a CTMS, for example in Microsoft® Excel or Microsoft® Project documents; however, in the future it is expected that more and more project-controlling functions will be integrated into the CTMS.

5.2.1 Sub-process: Clinical Study Management

5.2.1.1 Short Process Description

Beginning with the design and continuing throughout the conduct of a clinical study, it is essential to keep track of a large number of documents and data. This data originates from different parties such as (but not limited to) sponsor, authorities, third parties (e.g., CROs), sites, and subjects, and are available in different documents, (e.g., approvals of ethics committees, site qualification documents, monitoring reports, informed consent forms, and Serious Adverse Event (SAE) reports). A comprehensive CTMS combines the data in one place; consequently, it can be linked to various systems, for example, pharmacovigilance tracking, EDC systems, laboratory management systems, or Learning Management Systems (LMS).

Data can be manually transferred or directly uploaded from these systems into the CTMS. Manual data entry can be done remotely. Usually, key information necessary for trial oversight is maintained in the CTMS, while the detailed data is maintained in the respective specialized systems such as the safety database or DMS.

A comprehensive CTMS allows users to create and run customized detail or overview reports, and include alert functions for certain activities, metrics and/or milestones.

The continuous analysis of the collected data allows for the appropriate monitoring of study progress and compliance, and enables the stakeholders to make the necessary decisions.

5.2.1.2 Data and Risks Associated with the Process

Even though a significant part of the data has its origin in other databases, they are brought together in the CTMS. A risk assessment should be based on the description of the process conducted using the data available in the CTMS. As this data forms the basis for evaluations that can lead to relevant decisions, including study termination, the associated risk levels can range from medium to high. Because of this, it might be reasonable to split the CTMS into modules with high and medium risk. If a selected part of the CTMS is used in more than one process, the overall risk of this part is categorized as that of the process with the highest risk.

5.2.1.3 Validation Approach and Challenges

Development and validation of a CTMS should follow a module development life cycle. All software functionalities need to be validated and released for end user use.

Any additional customized functionality, for example special triggers and alerts, customized data reports or exports, and any interfaces to other databases, have to be validated against their specific requirements as well.

Note: for some study management data (e.g., monitoring visit reports), the CTMS can be the original database and this data is transferred to other systems linked to the CTMS, (e.g., the eTMF).

5.2.1.4 Typical Associated System Classes

Typically, CTMSs are classified as GAMP Category 4 or 5 depending on customization needs or whether a COTS system is used.

The majority of the validation activities are located in Layer II of the Validation Layer Model; however, there might be study specific requirements that need to be addressed, e.g., through changes to the system, the creation of interfaces, and/or special user defined customized reports. These activities are located in Layer III.

5.2.2 Sub-process: Project Management

5.2.2.1 Short Process Description

To perform a clinical study on the highest quality level, multiple processes/duties accomplished by several teams or team members need to go hand in hand. The sponsor “*takes responsibility for the initiation, management and/or financing*” (ICH E6(R2) [5]) of the trial, and often delegates the study management completely or partially to third parties (e.g., CRO; see also Chapter 4). Therefore, there is a chance that many interfaces might arise between companies, business units, and/or persons involved in the management of a study.

The selection of a qualified study project team and the monitoring of the study's progress are important. This requires detailed planning and a project risk assessment in the initiation phase, realization and monitoring of project tasks during the conduct of the study, and activities for terminating and closing of the project. The main phase (project control) is executed by means of a project plan oriented to the defined main processes and milestones outlined in this chapter (e.g., initiation, assembling the team, eCRF design and validation). Overall project management includes oversight of third party suppliers and partners.

5.2.2.2 Data and Risks Associated with the Process

Potential risks and daily challenges in project management are delays and failure to meet milestones. Although these are crucial business risks, the project management process itself does not have a direct impact on subject safety or data integrity for the following reasons:

- Systems or programs supporting project management tasks can help to control and regulate, but it is the project team that knows about the progress and difficulties in their project. Having a supporting system is beneficial but not crucial to the overall study results. It is more important that the project team is trained and qualified for their job.
- A project management tool is independent of data-collecting systems (e.g., eCRF, study database) or at least a separate part/page in the system, and its quality and function has no direct influence on study data.

In conclusion, project management tools in clinical studies have a low risk concerning subject safety and data integrity as long as they only support project management tasks. In cases where the project management system collects or uses data to control safety or data integrity tasks, the supported process has to be checked and the specific part of the project management system needs to be validated accordingly.

5.2.2.3 Validation Approach and Challenges

If the system supports any GCP-relevant aspects, it must be validated for those aspects. Often project management applications do not have any GCP risk, but are critical to the business. It is recommended to follow the same validation approach as for GCP systems to ensure fitness for business purposes. For such systems, a simplified approach may be chosen and should, after defining the requirements, mainly focus on:

- Verification of program functions (functional testing)
- User Acceptance Testing (UAT) to demonstrate fitness for purpose
- Adequate training of users
- Installation and maintenance of the system in the environment(s) needed

It is recommended that standard templates for clinical study project plans are created and maintained.

5.2.2.4 Typical Associated System Classes

Applications or tools used in project management can range from simple spreadsheets in table calculation programs and single desk solutions for project control, to enterprise versions of project management tools. The requirements for these systems are common across the industry and there are many software solutions available on the market.

Depending on the individual needs, these systems must be classified as:

- GAMP Category 3
 - E.g., non-configured single user project management applications or simple spreadsheets using standard simple calculations. This means a spreadsheet or spreadsheet template that uses native functions to make calculations in place of a hand calculator is typically Category 3. For example, a project manager might create a unique spreadsheet to do easy calculations or standard functions.
- GAMP Category 4
 - E.g., custom built enterprise project management applications or spreadsheets, or spreadsheet templates, with more complex calculation and configuration options. This means a spreadsheet template that requires the user to input tablet strength so that the application automatically branches to different cells to use strength-specific calculations based on this manual input. Such a simple operation would make the sheet Category 4, as it is effectively configured by the project manager before each use of the template.
- GAMP Category 5
 - E.g., custom-built or modified project management software or spreadsheets with nested logic and custom-built macros. This means a spreadsheet application that employs custom macros, sophisticated or nested logic, or lookup functions should be treated as Category 5.

Note: the product on which the application or spreadsheet is built (such as Microsoft® Excel) should be considered GAMP Category 1. For more information on spreadsheets and desktop applications, see *ISPE GAMP® 5, Appendix S3* [3].

5.2.3 Sub-process: Qualification of Project Team

5.2.3.1 Short Process Description

For reliability of results in clinical studies, it is of particular importance to work at the highest possible quality level. The accurate performance of all processes executed in the clinical study, (e.g., site monitoring processes), demands a high qualification of all team members (for training of site staff see Section 5.5.4 Sub-process: Site Initiation (Training)). This applies to the overall conduct of the clinical studies including processes, systems, and study specific requirements; therefore, all team members need to be evaluated concerning their qualifications and, where applicable, trained on relevant content, according to a training plan.

There is an ongoing debate as to whether or not this process should not only include training planning and execution, but also clear documentation of training success, (e.g., in form of a quiz). See also Section 5.13.2.

All training records need to be archived.

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5.2.3.2 Data and Risks Associated with the Process

The process itself and subsequently the risks concerning this process are divided into two parts. One is more organizational resulting from the need for a training plan and a defined process for conducting and evaluating training activities. The other is a more technical part, mainly concerning proper archiving of documents like CVs and training plans, tracking of the training and, if applicable, examination results.

The risk associated with this process is medium and has an impact on the quality of study conduct.

5.2.3.3 Validation Approach and Challenges

In contrast to the systems used in project management, there is an explicit requirement in GCP to provide the qualification of all people involved in conducting a study; thus, the risks associated with this process are GCP-relevant and all systems must be validated for their intended use (including tracking, archiving etc.).

Training personnel at all involved organizations (sponsor, clinical sites, CROs, etc.) is a challenge because it needs to be performed and documented, and the records transferred to the TMF. For example, when using externally hosted computer-based training (or training CDs shipped to the sites), the sites need to understand that all training data goes back to the sponsor for filing in the TMF, with data integrity maintained.

The approach for validation of these systems is rather standard (functional testing, UAT to demonstrate fitness for purpose, user training, controlled program installation and running), plus validation of the special functions required for training needs, evaluating, and archiving of all documents.

For training systems, the verification of program functions should consider the algorithms defined for evaluation of training needs. If these algorithms fit the requirements, the next step is functional testing of these program parts.

The documenting part of training systems and/or an independent archiving tool has to be validated regarding:

- Correct functions, e.g., correct mapping of training needs to personnel and trials (the system has to display an archive structure)
- Transfer of training documentation to the sponsor (e.g., if CDs with training materials are shipped to the sites)
- Long term storage, which is maintained on the basis of controlled processes (archiving, backup and restore, disaster recovery planning)

In addition to, or independent of the validation of the tools, a robust review process for training compliance by management should be in place for all training plans.

5.2.3.4 Typical Associated System Classes

The process of personnel training can be supported by systems with various complexity levels ranging from signed attendance lists in spreadsheet programs used to track the training sessions, to systems tracking and archiving CVs, training sessions and materials, and training plans (e.g., LMS or DMS), or systems in which the whole training session itself can be stored and versioned allowing the user to read and conduct the training on his or her own.

The system records the execution of the training, provides assessments, and creates and sends certificates if the test is passed. Access to other software systems like the eCRF can be linked to successful completion of the examination. These training systems can be found on CDs or eLearning Systems/LMS; therefore, mainly systems of the GAMP Category 3 (simple spreadsheets without macros) and 4 (e.g., standardized DMS or LMS) are in use.

5.3 Process: Electronic Data Capture System Life Cycle and Validation

5.3.1 Sub-process: EDC System Setup

5.3.1.1 Short Process Description

An Electronic Data Capture (EDC) system is used in clinical studies to electronically collect subject data that are within the scope of the trial protocol. This data is typically collected and documented during subject visits or taken from subject health records. They can cover a wide range of attributes, e.g., demographic data, concomitant diseases and medication, Adverse Events (AEs), laboratory analysis results, and data on examinations and medical procedures.

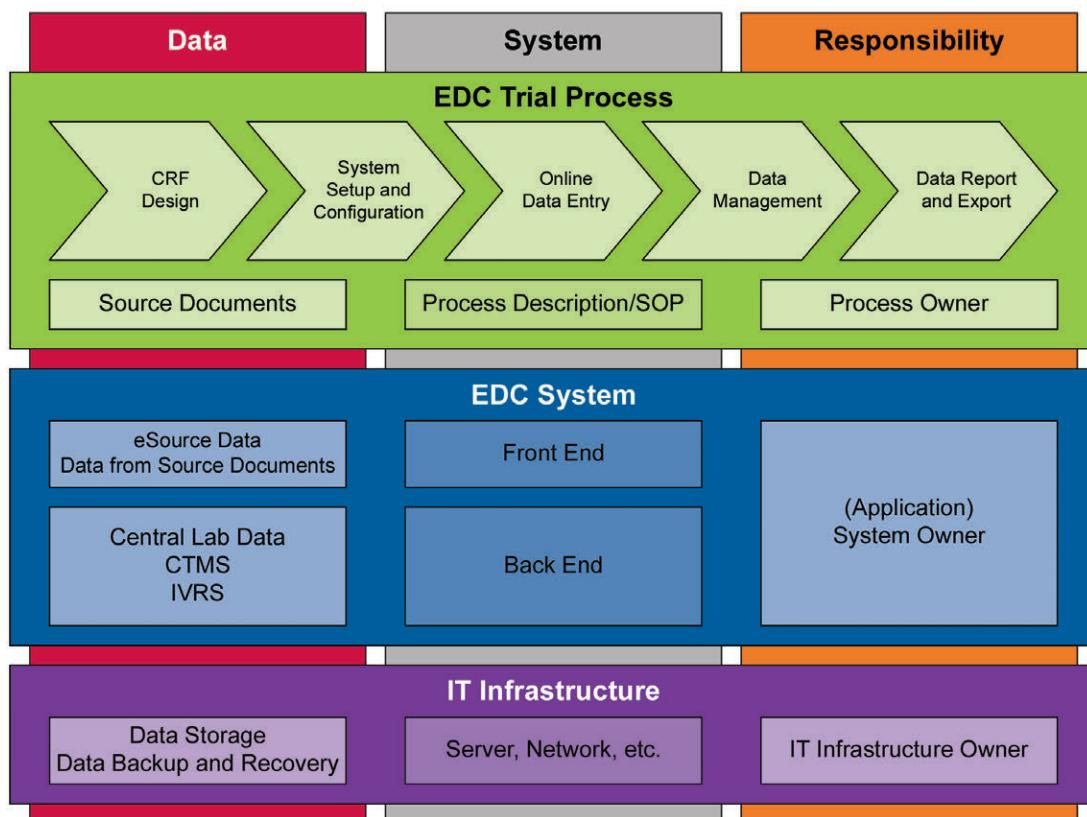
The trial-specific EDC setup is designed on the basis of a final trial-specific eCRF and contains the eCRF plus additional functionalities. The CRFs are created/adapted for each trial project based on the respective trial protocol and can contain complex calculations and data verification checks.

Furthermore, the eCRFs are often provided in multiple languages, including complex character sets, such as Chinese or Japanese.

To adequately support the business process (e.g., the data collection in a clinical study), the EDC system must provide the eCRFs to the participating sites and other staff involved; therefore, the EDC system, as a computerized system, consists of the EDC platform and the eCRFs.

Figure 5.1 shows the different levels of systems and processes on which a clinical study is based. The eCRF is part of the trial-specific frontend of the EDC system (blue level), which is based on a qualified infrastructure (purple level), and in use with trial-specific processes (green level).

Figure 5.1: A Schematic Model of an EDC Landscape with its Components Related to the Process, Data and Responsibilities



EDC systems are typically web-based and accessed by the local clinical study teams via a web browser. After a subject visit, the clinical study teams enter the subject data from the source documentation (such as patient health records) into the provided eCRFs followed by real time plausibility checks on the entered data.

Additionally, the data is continuously crosschecked by the monitoring team of the sponsor or CRO (source data verification). Any missing or incorrect data are followed up by the sponsor/CRO study team either directly or through the query functionality of the EDC system until resolution.

These workflows ensure reliable, efficient, and controlled communication between the clinical study sites and the sponsor/CRO study team and are audit trailed in the system.

As stated in ICH E6(R2) [5], the eCRF must be signed to document that the investigator confirms all observations recorded. If the CRFs are provided, completed, and signed electronically in an EDC system, the electronic signatures must comply with applicable regulations.

It is essential that the EDC system is stable and available at any time to ensure easy data entry without delay. Furthermore, it is important to consider the expectations of the anticipated end users. Particular considerations should be given to the support of local languages and a general ease of use, as otherwise the consistent use of the system and/or timely and correct entry of data may be jeopardized.

The eCRF should be always available; therefore, business continuity and disaster recovery processes are of special importance due to the potentially large number of continuously working end users at the sites.

An EDC system may provide the ability to interface with other clinical systems, e.g., CTMS or Interactive Voice Response System/Interactive Web Response System (IVR/IWR).

5.3.1.2 Data and Risks Associated with the Process

The data collected, stored, and calculated within an EDC system is often the source data of a clinical study; and as such there is a high risk to data integrity for the entire study. The system validation needs to address the principles of ALCOA+ (for further details see Chapter 6).

If the development of an eCRF is based on a paper Case Report Form (CRF), then the development of the CRF itself should ideally be finalized before translation into an eCRF and EDC setup.

However, it is common practice to combine CRF development and the development of the eCRF/EDC, thus mixing study-related discussions about the data to be collected (and often the study itself, potentially affecting the protocol) with the technical process of EDC setup. This often results in a long iterative development phase of the EDC system and requires proper change management before productive release of the system, or accepting the risk of undocumented changes with possible side effects, to keep both CRF and eCRF synchronized.

Specific risks associated with the EDC system setup process have to be evaluated considering three different aspects:

1. CRF: The CRF might be missing variables or contain incorrect variables. This aspect is a common risk of the process of paper/eCRF design and the risk is high. Of special importance is the capture of primary and secondary objective variables in a correct and reasonable manner.
2. EDC/Database: The EDC system inherits the typical risks of IT systems such as incorrect data input, data processing and storage, and data output.
3. Interfaces/Data Transfer: For each type of data transfer, automated, semi-automated, or manual, there is a potential risk of data loss or data change/corruption. Particularly for automated interfaces, it is advisable to maintain a separate life cycle including a complete validation life cycle.

5.3.1.3 Validation Approach and Challenges

Modern EDC systems are typically designed and qualified on a platform level, verifying and documenting that the required functionality to design and build eCRFs is available as expected. Study-specific eCRFs utilize the available functionality and require a significant amount of configuration and/or customization, e.g., for edit checks to reduce the likelihood of incorrect or inconsistent data.

The trial specific configuration or customization required to build the necessary eCRFs need to be validated in the context of each trial. Recently, eCRF libraries are being used to increase the reusability of eCRFs or parts thereof between trials and to reduce the trial-specific implementation effort. Moreover, automated approaches to generate eCRFs from the eCRF libraries are applied.

However, verification of the structure of the eCRF against the protocol is required to ensure that **all required data** is collected at **all specified time points needed** for the appropriate statistical analysis required by the trial protocol. The data is to be recorded contemporaneously during the subject visit.

Validation of the EDC system is required to ensure that access is controlled, all information from each field is stored correctly in the database, and all calculations and data entry checks are accurate.

Furthermore, since EDC systems store electronic records and typically use electronic signatures, compliance with Electronic Records/Electronic Signatures (ER/ES) regulations must be ensured. This includes verification of completeness and reliability of the audit trail.

All data, including data history and deleted data, must be available in the database and displayable for review to sites/investigators/auditors/inspectors in the eCRF. For all “actions,” the corresponding “timestamps” and “user identification” must be recorded and audit trailed. All timestamps should refer to a common or specified time zone.

Verification of the data itself, by using automated checks on plausibility and monitoring of the data against its source, is mandatory. Some checks cannot be automated as they involve qualified evaluations and expert judgment, requiring data management staff or medical monitors to look for complex relationships for instance between disease states and concomitant medications.

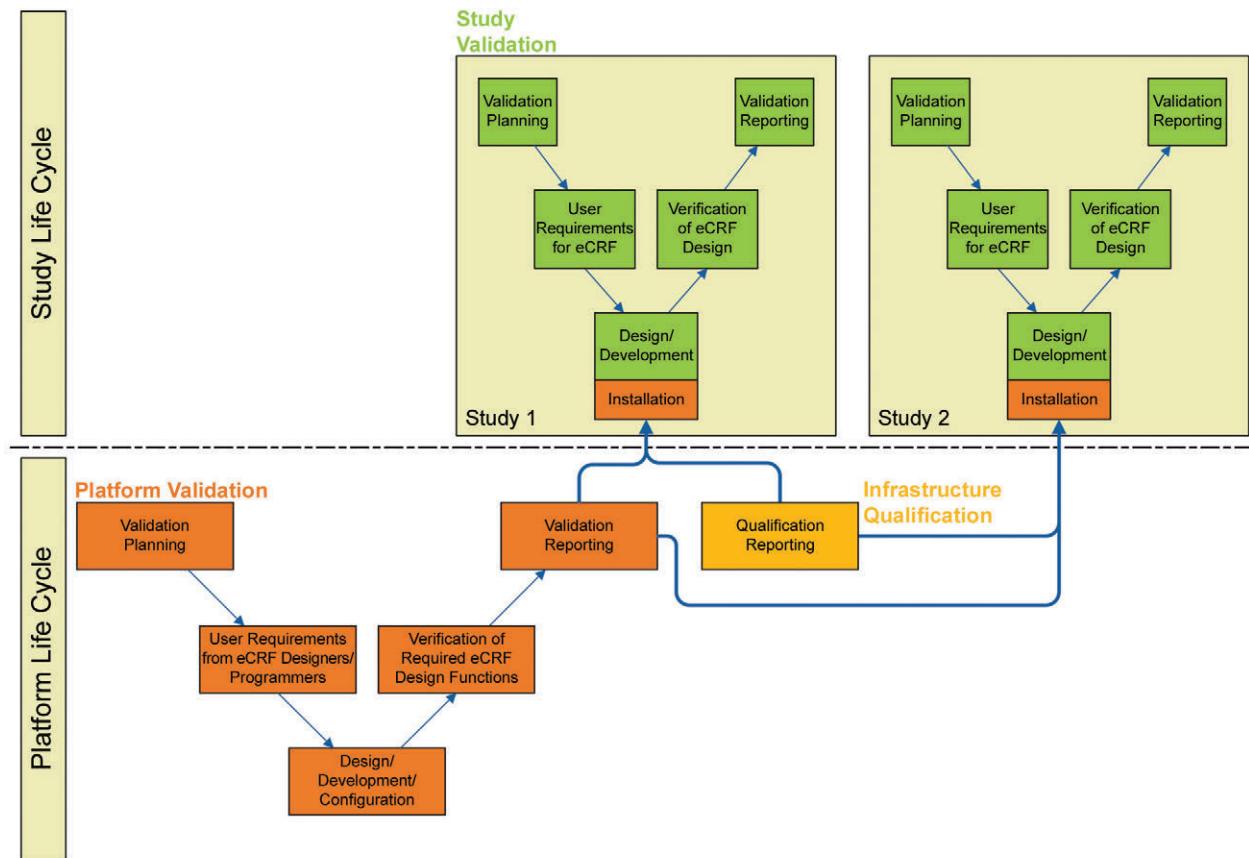
Whenever data is reviewed and approved, the reviewer/approver needs readable access to the changes and deletions of these data (audit trail) to allow further investigation and audit trail review when the integrity of a record is in question. For example, when a principal investigator reviews and approves the eCRF of a specific subject, the data changes and deletions relating to that subject eCRF should be visible on screen, including date, time, who performed the changes, and the reason for the change.

A qualified EDC platform provides the foundation for the subsequent eCRF design; however, as mentioned above, the eCRF design and the embedded plausibility checks require extensive validation as well.

Two life cycles, the platform life cycle and the study life cycle, must be considered when planning, validating, and operating an EDC system. Although both life cycles typically have development, test, and production environments, there should be a distinction made between the EDC platform and the trial-specific applications.

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Figure 5.2: Platform and Study Life Cycles

As illustrated in Figure 5.2, the platform life cycle is based on broad generic market requirements and needs. The study life cycle is based on the eCRF requirements of the sponsor of the particular clinical study as derived from the clinical study protocol.

The available COTS system platforms are often hosted by suppliers as Software as a Service (SaaS). If the EDC system is used as SaaS, parts of the validation activities are performed by the supplier and are often focused on the technical aspects, including the functions for the eCRF design and the deployment/upgrade of the system. In this scenario, it is essential for the sponsor to maintain close cooperation with the system supplier to ensure that the validated state of the system is not endangered by uncontrolled changes. Further guidance can be found in *ISPE GAMP® 5, Chapter 7, and Appendices M2 and M6* [3].

Last but not least, adequate training of the administrators and users on the EDC system functionality as well as the study-specific eCRF needs to be ensured and documented.

5.3.1.4 Typical Associated System Classes

The process of CRF development itself is often manual, requiring experienced personnel to develop the CRF on the basis of the treatment schedule and the study protocol.

The use of libraries of questions and fields is often helpful. Library software, ensuring consistent form definitions across all utilized EDC systems, or a library within the EDC core system itself can be used. Using known, industry- and regulatory-accepted standards like Clinical Data Acquisition Standard Harmonization (CDASH) for CRF design may also be considered.

The process of combining and inserting all required questions and fields in the CRF needed for the statistical analysis is a manual process. Frequently document management systems are used to ensure proper versioning of the CRF libraries.

Typically, EDC platforms are either complex COTS systems (GAMP Category 4) or custom-developed (GAMP Category 5). Based on the system complexity, it may be advisable to classify further additional elements of the system as GAMP Category 4 (e.g., configurable workflows that do not require programming).

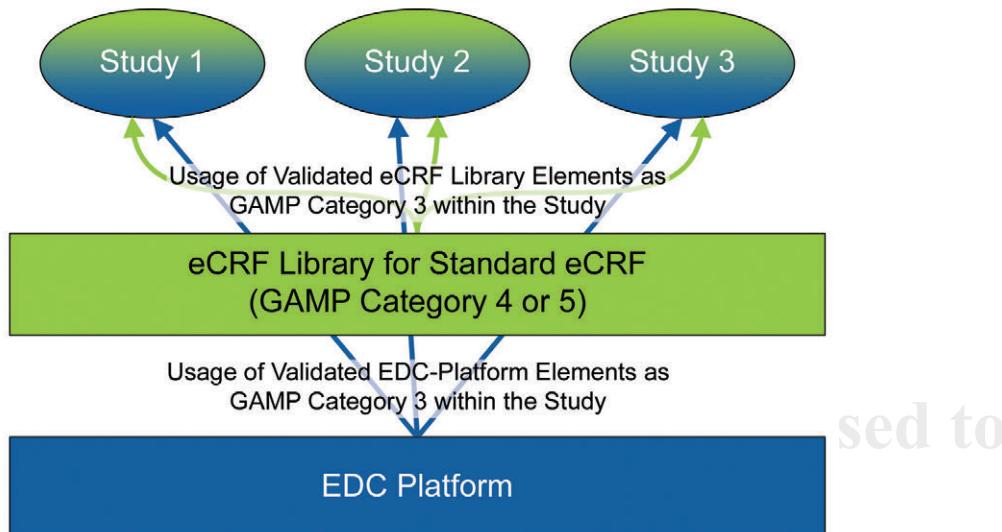
EDC systems are often supported by CRF library systems that are either COTS systems (GAMP Category 4) or custom developed (GAMP Category 5). Once these library systems are validated, they can store validated, versioned eCRFs. These eCRFs then can be reused with minimal effort, significantly reducing EDC setup and validation efforts.

Depending on how extensively eCRF libraries are used, the eCRF can be GAMP Category 5, 4, or 3. A useful strategy is to define the EDC system as Category 5 and reduce the validation effort in alignment with a detailed risk analysis by defining different categories. These categories may be:

- Review of an already validated part (Category 3)
- Additional testing of configuration items (Category 4)
- Validation of new elements (Category 5)

Figure 5.3 shows how a qualified platform and eCRF library elements allow this approach.

Figure 5.3: GAMP Category Classification of eCRF Libraries



5.3.2 Sub-process: EDC System Maintenance Phase

5.3.2.1 Short Process Description

As mid-trial changes are likely to be the norm and not the exception, standardized and robust processes for change/configuration management should be defined as part of the overall management system for the EDC/trial system life cycle. These processes need to be able to support a range of possible modifications from a small change to a complete eCRF redesign within the system. It is essential that the validation/technical team can assess the nature and impact of the change, document the resulting risks, and estimate the required effort quickly to support the planning of the mid-trial change. The implementation of the mid-trial change should not jeopardize the validated state of the overall system.

Unlike GMP, there is no regulatory requirement for changes to clinical computer systems before they go live to be approved by Quality Assurance; although this should be considered as good practice for high impact changes. This emphasizes the need for efficient change/configuration management procedures. For changes with minor impact, a peer review by qualified personnel can also be sufficient, e.g., the process owner.

5.3.2.2 Data and Risks Associated with the Process

System design and maintenance need to be considered during the risk assessment and design phase. Possible means to address the risks resulting from the multiple organizations (sites, CROs, and sponsor) include:

- Use of a controlled IT infrastructure (e.g., qualified server)
- Suitably qualified and trained people for the implementation process
- Use of technology that can be used independently from the system on which the data is entered (e.g., web-based, using data validation checks on the client and/or server side)
- Specification of fundamental system requirements (e.g., supported browser software and version) as part of the end user training
- Establishment of good lines of communication to end users for support with technology and other issues
- Availability and use of a well-organized support structure (e.g., according to ITIL® [44])

The validation team should be aware that testing of the EDC system would not cover all possible scenarios. Therefore, particular care should be taken during the system design phase to avoid imposing limitations with regards to browser software, underlying Operating System (OS), Java, .net framework, or even the type of computer devices used (e.g., tablets, smartphones) to access the EDC system. Such considerations should be documented in the formal risk assessment and form the basis for the test strategy.

Further guidance can be found in the *ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Operation of GxP Computerized Systems* [45].

5.3.2.3 Validation Approach and Challenges

As study and EDC platform life cycles may be independent from each other, the design of the EDC system must consider the following question at the planning stage:

Can the EDC platform be updated or must it remain stable during the conduct of a trial?

An overview showing the advantages and disadvantages of updating an EDC platform during the life time of the trial-specific system is shown in Table 5.1.

Table 5.1: Overview of EDC Platform Update

Strategy	Advantages	Disadvantages
Keep the EDC platform stable during the life time of the trial-specific system	Reduction of risk to the eCRF, potential (study-specific) interfaces and data integrity	Does not address IT security risks or technology advancements for the duration of the trial
Update the EDC platform during the life time of the trial-specific system	Permission for installation of IT security patches or technology advancements	May lead to a significant number of deployments in different versions and therefore increases the testing, IT support, and maintenance efforts. This increases the risk to data integrity.

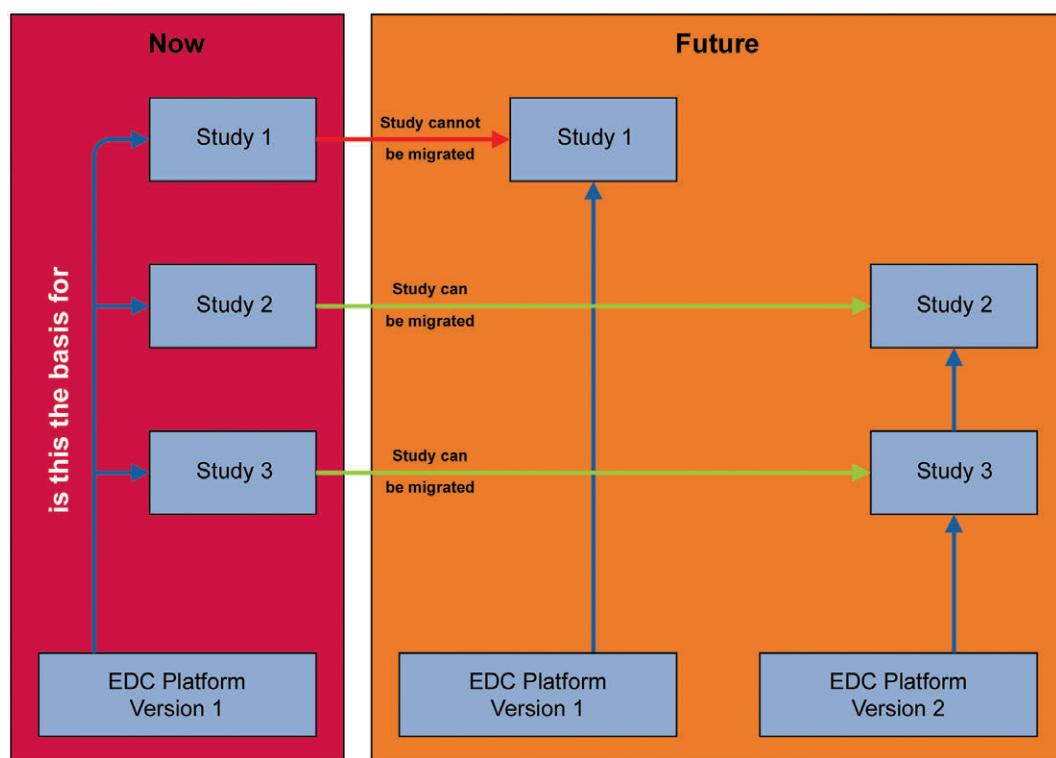
If the decision has been made to update the EDC platform an impact analysis must be conducted to consider:

- Which features will be changed, added or removed
- Which approach should be adopted for risk-based testing of all affected trial configurations

It is important to document the results of the impact analysis and the testing approach to justify the upgrade decision.

Figure 5.4 outlines the key steps and a potential outcome for an EDC platform upgrade.

Figure 5.4: Potential Upgrade Scenario for an EDC Platform Leading to Multiple EDC Platforms Supporting the ongoing Studies (such a scenario may increase the support effort significantly)



To minimize the support and maintenance efforts, the teams should aim to upgrade as many studies as possible.

A first analysis of the platform upgrade should be independent of the individual affected trials, e.g., if the new version only provides bug fixes, it is very likely that they will not negatively impact any on-going trials. However, if features are significantly changed, removed, or new features are added, the analysis might need to consider study-specific aspects in more detail. The decision to upgrade or to remain on an older version of the EDC platform must be well justified (e.g., study is due to end very soon) and documented.

With each core system setup or study-specific eCRF change, adequate retraining of administrators' and users' needs to be ensured; therefore, a decision concerning training needs and training format (e.g., is formal training required or is a newsletter enough?) for internal and external users is necessary.

This approach entails:

- An independent versioning and documentation of the platform
- An independent versioning and documentation of each study

The study version needs to refer to the then current platform version. Changes in the study do not affect the platform and can be done independently from the platform life cycle. However, changes of the platform version and its release into production require a documented change for each study, including at least the following steps:

- Reference to the new platform version number
- Analysis of the potential impact of the platform changes on study functionalities
- Testing of functionalities with an identified impact and risk

The following example highlights the need to maintain different trials on different versions simultaneously with the resulting challenges:

- MedDRA [46] is a coding dictionary for regulatory use and is updated twice a year. When different studies using the same platform require different MedDRA versions, different approaches can be applied:
 - The platform could provide all MedDRA versions, with an update to the MedDRA version performed twice a year (updating the version, verifying/testing that the new version is correctly implemented).

This could result in a change of the platform and changes to the study systems, requiring at least an impact analysis focusing on how the new MedDRA version in the platform affects each study. For studies that will adopt the updated version, it needs to be verified/tested that the study now uses the new MedDRA version.

- The MedDRA version could be maintained as part of the study database; twice a year all studies that need the updated version would then require a change (updating the version, verifying/testing that the new version is correctly implemented).

This example shows that there are various options for maintaining the systems in a validated state. All approaches have one thing in common: since the system ownership of the different platforms and studies usually reside with different persons, there is a need to define an owner of the landscape to make sure that these risks are owned and addressed.

5.4 Process: Electronic Patient Reported Outcome System Life Cycle and Validation

5.4.1 Short Process Description

Electronic Patient Reported Outcome (ePRO) systems are used to obtain clinical data directly from the patient. This includes patient diaries employed to obtain frequent assessments over a period of time. Typically, this data is collected via an Interactive Response Technology (IRT) system or via mobile computing platform such as smartphones or tablet computers. Additionally, wearables can be used to collect data continuously from the patient. Other measurement instruments (e.g., for blood sugar) could also be interfaced with an ePRO system.

ePRO technologies are used either on a continuous basis or on site to collect data via data entry forms completed by the patients during their scheduled visits. Examples are quality of life questionnaires or patient diaries on drug use.

5.4.2 Data and Risks Associated with the Process

The level of risk depends on what data is collected and how.

If data from patient diaries is used for patient safety assessments and/or primary and secondary endpoints of the study, a direct risk concerning subject safety and data integrity is clearly present. On the other hand, a collection of quality-of-life data is comparatively low risk.

If data is obtained from wearables or medical devices, such as smartphone-based electrocardiographs approved by the regulators, a wide variety of controls are required, as with other sophisticated electronic medical devices.

Arising potential risks could be:

- Unwillingness to use the electronic system by the patient (e.g., elderly patients)
- Inconsistency in localization (translation into multiple languages)
- Lack of oversight by the site/investigator
- Untimely or incorrect recording of data
- Managing ePRO software on a variety of operating systems at different version levels on many different devices
- Access control and security in a Bring Your Own Device (BYOD) setting

Depending on the data collected, the same risks and problems as in EDC systems may need to be considered. If the data is collected at a site in a supervised situation, compliance is less of an issue as the systems used are provided in a more controlled environment than the smartphone of the patient.

Generally, data privacy/protection aspects must be considered in all ePRO solutions.

5.4.3 Validation Approach and Challenges

The validation approach for an ePRO solution is often very similar to the validation approach of an EDC system as it serves the same purpose of clinical data collection. Often ePRO solutions are GAMP Category 4; however, due to the project nature of clinical trials, customizations are common. Also, integration with other systems (e.g., EDC, IRT) is often customized.

As more and more ePRO systems are designed as mobile applications, the guidance provided in the *ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Regulated Mobile Applications* [47] should be considered in the validation approach.

5.5 Process: Site/Partner Qualification

5.5.1 Sub-process: Selection and Qualification of Partners/Suppliers

5.5.1.1 Short Process Description

The selection of qualified sites and partners, including the clinical investigators, is crucial for the quality of a clinical study.

The selection and qualification process consist of all aspects of contract management as well as identity- and authorization-management activities. The site initiation activities also require study-specific training and perhaps an investigator meeting. Once qualification activities are complete, including receipt of regulatory and ethical approvals, the site is opened/activated and can start recruiting subjects.

According to ICH E6(R2) [5], the sponsor is required to evaluate the availability of resources and the qualification of persons at the site involved in the conduct of the clinical study.

Site qualification mainly applies to the potential site itself (resources), including local laboratories and pharmacies, and the involved investigators (education, training, experience). Corresponding documents to confirm qualification, e.g., CVs of investigators, are essential for IRB/EC submission and study approval, and need to be filed in the ISF.

Usually, the sponsor or the CRO will check the qualification of the site during a pre-study visit or by qualification questionnaires.

Other partners might include:

- CROs (data management, statistics, etc. or full service) [5]
- Monitors [5]
- Auditors [5]
- Medical experts [5]
- Central laboratories
- Pharmacies
- Clinical supply logistics partners
- Manufacturer of IMPs

These partners need to be qualified, for example by conducting audits or by obtaining qualification questionnaires. All qualification measures must be completed before study initiation (for audits, see Section 5.13.1).

5.5.1.2 Data and Risks Associated with the Process

Selection and qualification of partners/suppliers is associated with an indirect risk to subject safety and data integrity.

Potential risks arising from sites and investigators could be:

- Incorrectly assessed ability to recruit the required number of suitable subjects
- Low recruitment of subjects and data collection behind schedule due to insufficient time or competing studies
- Inadequate number of qualified staff
- Inadequate facilities (e.g., local laboratories), including possible failure to provide compatible infrastructure or failure to assure data integrity/information security

Potential risks arising from partners could be:

- Non-detection of diverse deficiencies during study conduct and data collection
- Poorly defined processes resulting in difficulties for the sites to comply
- Change of monitors resulting in re-qualification and possible interruption of supervision of sites
- Insufficient qualification of monitors resulting in e.g., Source Data Verification (SDV) deviating from the monitoring plan, inadequate monitoring visit reports

- Inadequate laboratory data due to non-validated methods/non-validated systems
- Inadequate controls or processes resulting in incorrect/delayed shipment of investigational product
- Staff turnover in general

Any or all of these issues might delay the study's progress, leading to prolonged study duration. Also, they might result in the transfer of incomplete or incorrect information to the sponsor.

In order to minimize these risks, these aspects must be checked during the qualification phase. Additionally, there are other processes (e.g., on-site audit) during study conduct that can monitor and possibly correct deficiencies.

The results of qualification and audit activities as well as the final assessment with justification need to be documented in a separate report and filed in the TMF.

The quality of sites and investigators will be checked by an Independent Ethics Committee (IEC) prior to the study start, but this does not apply to the qualification of suppliers/partners; therefore, it is mandatory to have corresponding SOPs for partner qualification in place.

5.5.1.3 Validation Approach and Challenges

Because the corresponding documents need to be stored and maintained, for example in the CTMS and/or TMF, refer to Section 5.1 and Section 5.12.3.

5.5.1.4 Typical Associated System Classes

Because the documents generated by this process are normally stored and maintained in the CTMS and/or TMF, refer to Section 5.1 and Section 5.12.3.

5.5.2 Sub-process: Contract Management

5.5.2.1 Short Process Description

Negotiation and approvals of contracts between sponsors, sites, and partners must be concluded and documented after qualification but before the first study activities commence. Contracts must contain clear descriptions of roles and responsibilities.

5.5.2.2 Data and Risks Associated with the Process

Normally, the first step is to sign a mutual non-disclosure agreement between sponsor, sites, and partners. Thereafter, an exchange of confidential study information will take place in order to discuss possible cooperation.

Where there is agreement and a site or partner has been qualified, the final contract should cover at least the following points on the basis of the study protocol:

- Determination of:
 - Applicable guidelines and laws
 - Timelines

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- Arrangements on:
 - Delegation and distribution of tasks and obligations
 - Financial matters [5]

In conclusion, contract management itself does not pose any risks to subject safety and data integrity because during this process the only documents to be stored and maintained, e.g., in a CTMS, have no impact on future subject treatment and data collection.

Nevertheless, site contracts are part of the submission to IRB/EC for study approval, so there is a business risk in the sense that incorrect or poorly maintained documents could jeopardize the approval of the study.

This process also needs to be defined in appropriate SOPs.

5.5.2.3 Validation Approach and Challenges

Because the corresponding documents have to be stored and maintained, for example in a CTMS and/or TMF, refer to Section 5.1 Process: Study Protocol and Submission for Approval and Section 5.12.3 Sub-process: Creation of the TMF and ISF.

5.5.2.4 Typical Associated System Classes

Because the documents generated by this process are normally stored and maintained in a CTMS and/or TMF, refer to Section 5.1 Process: Study Protocol and Submission for Approval and Section 5.12.3 Creation of the TMF and ISF.

5.5.3 Sub-process: Identity and Authorization Management

5.5.3.1 Short Process Description

Systems supporting clinical studies may be used by individuals situated in multiple organizations and locations in a variety of roles. To safeguard data integrity and to meet regulatory expectations, a robust process for requesting, granting, reviewing, and revoking user access and user rights is required. It should be noted that the identity of each user requires verification prior to the training and assignment of user access.

Changes to user accounts and roles are very frequent. Throughout the study life cycle these changes are needed, due to e.g., site assignment changes, staff turnover, study staff assignments, and study closure activities. This process needs to be based on the principle of the least privilege – user accounts should only provide those privileges that are essential to that user's work.

These roles are often defined on a trial-by-trial basis and must be reviewed periodically.

It is of key importance that user account creation and changes of user rights are recorded in the system's audit trail. This audit trail can be instrumental in the periodic review process of user accounts.

In addition to the GCP regulations, identity and authorization management should address the organizational data classification needs (e.g., secret, confidential, public) as well as applicable data privacy regulations.

5.5.3.2 Data and Risks Associated with the Process

The risks associated with users directly entering or altering data in a system need to be addressed as this data forms the foundation for outcomes of the study and the resulting new knowledge, treatment regimens, or even innovative, new medicinal products.

These risks can be mitigated with documented processes addressing:

- User access provisioning, including verification of identity and user role
- Use of individual user names/IDs and unique passwords
- Allocation of specific user rights limited to the duties of a person/role
- User access history
- Periodic review of access rights

Individual passwords ensure that only appropriately trained people assigned to a particular study and its corresponding systems are able to enter, modify, or delete data. Prior to granting any access, the identity of each user needs to be verified regardless of whether the user belongs to a site, to the sponsor, or to a third party.

Ideally, an initial password is generated by the system and sent to the user with the instruction to log in and change the password immediately. A policy should be in place that gives additional instructions with regard to safe passwords such as complexity, minimum amount of characters, and use of lower case and capital letters, numbers, and special characters.

Additionally, passwords should expire within a set period of time so that the user is forced to set a new password. User accounts should be locked by the system after multiple incorrect entries of the password. New passwords should be significantly different from previous ones since passwords are more secure the greater their variability and non-similarity.

The allocation of specific user rights linked to the tasks that need to be performed from an individual during a study helps to minimize accidental or intended alteration of data.

Following the principle of least privilege, each user should only have the rights needed to fulfill their role. Since there are often many people involved that perform identical tasks even in different projects, the use of role concepts or user groups helps to minimize the workload involved in user management as well as to reduce the risk in connection with mistakenly assigning wrong functions or not assigning all needed functions.

These role concepts can be decided and set based on the organizational structure of the studies for which the systems will be used, study nurses, investigators, data managers etc. When using role concepts, it should always be possible to adjust the settings of specific users when certain tasks need to be added or removed within a project.

Because different organizations and different roles are involved in each study, it is mandatory to periodically review the user accounts. This means verifying study assignments and role concepts to ensure that user access is current and appropriate. Special attention must be given to privileged accounts, e.g., administrator accounts.

Based on the fact that each individual should only be assigned to a study or task as long as they are actually involved, user access history should be kept. This ensures that the responsibility for entered, corrected, or altered data can be identified at any time during the study's life cycle.

5.5.3.3 Validation Approach and Challenges

The allocation of individuals will most likely differ from study to study while the role concepts might remain constant; therefore, role concepts should be developed, set, and tested independently from a study. Once they are validated, they can be inherited for the same user groups in different studies within the EDC system.

Prior to the start of a study project, the role concepts should be reviewed and, if necessary, adapted to the project. If deviations from the validated user role concepts occur, the changes need to be tested within the concerned project before study start-up.

Additionally, rules for passwords should be set to enforce strong passwords and avoid the reuse of passwords with only minimal changes. Because customer requirements are different in regards to their password policies, these rules, such as complexity, number, and kind of characters, are usually set and tested separately for each study project.

Identification of the individuals granted access to the study is a crucial step and part of clinical study management. Only persons involved in the project should be given access to the study at sponsor, CRO, suppliers, or sites:

- Involvement of sponsor, CRO, and supplier staff in the project is tracked in the study specific responsibility list.
- Site staff are identified:
 - In Phase I – IV studies during the process of site qualification and for ethics committee approval via a CV and detailed questionnaires. A contract with the site is in place and a delegation log is maintained at the site.
 - In non-interventional studies via proper contracting. The principle investigator is identified with his/her signature. For each additional person, the principle investigator signs the access request, thereby identifying that person.
- Patients (for e.g., ePROs) are identified via site staff and obtain access and password information through study site personnel.

5.5.3.4 Typical Associated System Classes

The validation of passwords and role concepts customarily takes part in Layer II of the Validation Layer Model with the intention of inheriting these concepts. Study-specific changes need to be validated in Layer III of the model.

Usually, the validation approach should follow the requirements of GAMP Category 4 for configurable software.

Study portals providing a single sign-on function must be validated according to risk and are typically GAMP Category 5.

5.5.4 Sub-process: Site Initiation (training)

5.5.4.1 Short Process Description

When all ethical and regulatory requirements (positive vote of the responsible ethics committee(s) and approval by the competent authority(ies)) are fulfilled, a site can be initiated. During the initiation visit, the study staff at the site will be trained on:

- The study protocol and GCP
- Documentation requirements, especially reporting of AEs/SAEs
- Data entry and handling of the EDC system
- Handling of investigational products
- Other study specifics

In addition, the ISF will be provided, where the site's relevant study documents will be filed.

After a successful initiation visit, the ISF and required approvals are available, and when access to the IMPs and the eCRF is given, the site is able to recruit and treat subjects according to the study protocol and to collect the respective subject data.

5.5.4.2 Data and Risks Associated with the Process

The content and all open issues arising during the initiation visit are to be documented in the initiation visit report. All training needs to be recorded, and certified copies of the training records must be filed in the TMF.

The risks associated with incomplete or insufficient training include:

- Insufficient adherence to the study protocol resulting in a high number of protocol violations and/or drop-outs and, in the worst case, incorrect treatments
- Non-adherence to AE/SAE reporting time frames (see Section 5.9 Process: SAE Reporting)
- Inaccurate and delayed data entry resulting in poor data quality
- Incomplete documentation and filing

These risks have a low impact on data integrity and subject safety at the time of initiation, but may have a high impact later during subject treatment and data collection (see Section 5.7).

All documents generated to record the completion of the initiation visit are often stored and maintained in the CTMS. In addition, the corresponding entry within the CTMS or a similar system needs to be performed in order to signal that the respective site is ready to recruit subjects.

5.5.4.3 Validation Approach and Challenges

Because the corresponding documents are normally stored and maintained e.g., in a CTMS or TMF, refer to Section 5.1 and Section 5.12.3.

5.5.4.4 Typical Associated System Classes

Because the documents generated by this process are normally stored and maintained in a CTMS and/or TMF, refer to Section 5.1 and Section 5.12.3.

5.6 Process: Investigational Medicinal Product Management

The Investigational Medicinal Product (IMP) is manufactured, released, and shipped following GMP and Good Distribution Practice (GDP) regulations. Tracking the IMP during distribution and use is a regulatory requirement. Processes for the recovery and the destruction of any excess or expired IMP must be in place. If applicable, any auxiliary material, e.g., syringes, applicators etc. distributed by the sponsor must be controlled as well.

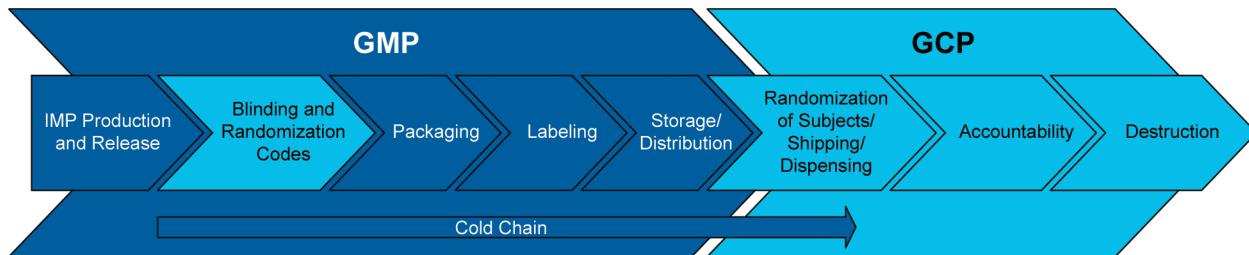
For processes related to a clinical study GxP standards have to be applied. The requirements related to IMP management are mainly described in ICH E6(R2) [5], and Sections 5.13 “Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)” and 5.14 “Supplying and Handling Investigational Product(s)”. According to these references, ICH requires that (inter)national GMP principles have to be followed for IMP manufacturing, although the legal status of ICH E6(R2) varies from country to country (e.g., scientific guideline or national law) [5].

For the GMP area, 21 CFR Part 11 (USA) [8] and Annex 11 (EU) [26] requirements must be met. For clarity's sake, typical GMP-related systems and processes within a clinical study will be referenced in this Guide but these systems are out of scope regarding validation from the GCP perspective.

Therefore, this section focuses on GCP and specific requirements for drug development as well as possible related risks within IMP management processes in comparison to the manufacturing of medicinal products.

An overview of the IMP management-related sub-processes and associated systems is given in Figure 5.5.

Figure 5.5: IMP Life Cycle



In general, GMP requirements apply to IMPs in the same way they apply to medicinal products for commercial use; however, of particular importance are the following points as they differ significantly from the commercial GMP business processes.

- **Global Environment versus Country-Specific Requirements**

Clinical studies are mostly planned for and conducted in a global environment. Although the ICH E6 [5] requirements apply worldwide, country-specific regulations for GMP and GCP may differ in some details (e.g., IMP/IND is country specific).

Example: Responsibilities/Accountabilities

European Union Directives require a Qualified Person (QP) for product release [48]. In this context, the QP is responsible for manufacturing and quality control, which need to be performed in compliance with the laws in force and (as applicable) in accordance with the marketing authorization. This requirement is an additional precondition for a manufacturing authorization/manufacturing and import license in the EU. In contrast, the QP requirement is not part of the FDA regulations [49].

Example: GMP Applicability Within the Clinical Study Phases

For Phase I studies the FDA does not demand fulfillment of GMP requirements [49], but GMP standards must be met for all clinical study phases in the European Union [48]. Nevertheless, data from Phase I is often subject to FDA inspections; therefore, comprehensive documentation is required e.g., Good Scientific Practice should be applied.

Within the trial phases requirements may differ. For example, in Phase 1, calibration, maintenance, and system suitability testing for analytical devices may be sufficient according to FDA [50]; whereas in Phase III method validation becomes mandatory because generally binding GMP requirements apply [51]. See ICH Q8(R2) for further information in terms of the contents of a regulatory submission [52].

- **IMP, Placebo, and Comparator**

A condition for conducting a clinical study is that the potential patient benefits must justify the calculated risks to the patient. In the majority of clinical studies, the significance of the IMP is demonstrated by the use of a placebo (no active pharmaceutical ingredient) and a comparator product to show that the new IMP has a significantly enhanced effect. Therefore, it is essential to avoid mix-ups between those three entities within the supply chain in connection with randomization and (double) blinding during the packaging process.

- **Increased Complexity of Change Management**

Since the new IMP is often under development during the clinical development program, the consistency of product quality is impacted by increasing production volumes, changing dosage forms and product specifications as well as expiry dates within and throughout the trial phases.

- **Increased Subject Risk**

In principle, there is a higher risk for subjects/trial subjects in a clinical study utilizing a new IMP in comparison to an established commercial product, because of the IMP's development status.

5.6.1 Sub-process: IMP Sponsor Batch Release

5.6.1.1 Short Process Description

An important aspect of IMP management is the sufficient production of IMP to ensure appropriate shipment and availability in the trial sites. Although many responsibilities may be transferred to third parties, the final accountability for clinical studies, which includes the integrity (quality) of the trial data, remains with the sponsor. Therefore, the release of each production batch by the QP or other QA reviewer/approver and subsequently by the sponsor is a fundamental requirement.

It is possible that after the shipment to the sites a second release is needed, e.g., if temperature controls and monitoring is mandatory.

As mentioned, the IMP is often under development during the conduct of the clinical study. Many specifications for analytical testing and manufacturing are not fully known at the beginning of the trial and those that are known are changing frequently due to the development status.

There is a need to update the preliminary specifications in a controlled manner until the final product authorization is obtained. These specifications are defined, e.g., in the Investigational Medicinal Product Dossier (IMPD / IMP Dossier), at the beginning of a trial program (Phase I to Phase III). All changes must be reported to the respected authorities without delay.

The sponsor's responsibilities and accountabilities for batch releases may differ in a global environment. In general, the local QP or QA reviewer and approver must provide written confirmation that all country-specific regulatory requirements according to GMP have been met before authorization of the IMP for delivery to the trial sites.

5.6.1.2 Data and Risks Associated with the Process

Almost all data and related records for the authorization described in this chapter are critical because they are not only the basis of the batch release within clinical studies but are also included in the final submission; therefore, the associated risk is high.

There is no impact on the Clinical Study Report (CSR), and the risks in this chapter are mostly attributed to the development state of the IMP.

Trial-specific batches of IMP are released based on the specification stated in the IMPD and require:

- Approved IMP Order
- Certificate of Analysis
- Certificate of Compliance

Quality Control Data: Certificate of Analysis

The Certificate of Analysis (CoA) is the sponsor's confirmation that packaging information and analytical results (e.g., raw materials or stability data) of the IMP are in accordance with the product specification file. Worst-case scenarios in this area include:

- Changes in specifications are not comprehensively tracked and/or documented, or documentation is deficient (e.g., versioning). This might result in erroneous product release of a batch for the clinical study that should have been rejected.
- Expiry date of a product is determined by stability trials. Environmental conditions during those studies have to be monitored, evaluated, and documented to identify potential excursions. A typical worst-case scenario is the expiration of the IMP during trial conduct without it being noticed.

Data from Manufacturing Processes: Certificate of Compliance

The Certificate of Compliance (CoC) includes manufacturing formulas, conditions, and in-process controls, as well as labeling and packaging information. With the CoC the sponsor ensures that the product was manufactured according to GMP requirements. Worst cases may be:

- Insufficient knowledge of process parameters due to the early development processes leading to inadequate specifications, a lack of standardization possibilities, and deficient validation of the manufacturing processes.
- Packaging or labeling information may unblind the trial.

Batch Certification

For the certification of the IMP batch the CoC and the CoA need to be signed/approved by the person responsible as the Head of Manufacturing and the Head of Quality Control, or, for example, the Qualified Person.

The Batch Certificate contains additional clinically-related data like the clinical study authorization number and sponsor protocol code number for the trial in which the shipped batch will be used. The persons responsible for batch certification have to ensure that all relevant GMP requirements including the current specifications according to the IMPD (which are country specific) are met.

Potential risks may be:

- Products not intended for the trial may be given to the subject
- Products may be given to the subject although they do not meet all specifications of the IMPD

5.6.1.3 Validation Approach and Challenges

In general, all manufacturing steps supported by computerized systems should be performed using validated processes and qualified equipment as recommended (e.g., according to ISPE GAMP® 5 [3]).

Existing documentation and the involvement of qualified third parties can help to leverage the validation effort and ongoing quality control. Appropriate documented training should be provided in such cases, along with clear definitions of responsibilities.

All relevant changes to the specifications or quality and subject safety-relevant processes must be justified, well documented, and controls should be in place to ensure that the regulatory agencies are informed of any pertinent mid-study changes.

Multiple interdependencies, process changes, and quality attributes may lead to subsequent process-related changes (e.g., protocol amendments) and/or changes to computerized systems and their validation. As a result, the affected documentation needs to be revised to ensure the continued IMP release to the sites. This requires an effective impact assessment and resulting risk communication to all involved business partners, including third parties.

The risk assessment should have a special focus on the following points:

- Regulatory requirements:
 - There are different drug development stages. GMP requirements in terms of qualification and validation are not mandatory for all of these stages especially when the IMP is not given to humans. Development and GMP aspects should be logically separated so that changes in one of these aspects do not affect the other, and so that intermingling of the different standards is prevented.
 - The underlying regulatory requirements (e.g., predicate rules) for electronic records and signatures should be identified and fulfilled. And the essential question concerning what raw data and records will be generated, and whether these are part of batch release and/or submission, should be answered taking into consideration what data and related processes are expected to be subject to frequent changes.
- Complexity of the system supporting batch release/submission-relevant processes:
 - In what environment is the system used: local or global?In a global environment, it is recommended to install an identical system version with site-specific configurations in order to reduce the overall validation effort. This is especially recommended if the processes (workflows) are harmonized, as this avoids different accountabilities/responsibilities leading to different workflows as a result of local regulatory requirements.

One challenge in this context is to keep the different instances synchronized. Changes in one system automatically affect the other instance(s) resulting in longer decision-making processes due to time-consuming arrangements. On the other hand, this concept may be acceptable as it may lead to lower maintenance and administration costs.

- Systems used in processes for clinical supply have to be flexible in terms of changes resulting from the pharmaceutical development program. Often, customized solutions for these systems have to be applied leading to more complex and more rigorous validation and qualification compared to a commercial manufacturing system.
- Interfaces to outsourcing partners

In most research and development and clinical study projects, outsourcing partners like third party manufacturers/laboratories as well as CROs are involved in the management of development, manufacturing and/or testing of the IMP. Access by the respective partner to critical systems should be under control and limited.

When the outsourcing partner generates critical data, it needs to be assured that these systems are appropriately qualified and validated, including the interfaces and processes.

5.6.1.4 Typical Associated System Classes

Almost all LIMS and chromatography data systems are classified as GAMP Category 4 or Category 5. For further information refer to *ISPE GAMP® 5* [3].

5.6.2 Sub-process: IMP Labeling/Packaging

5.6.2.1 Short Process Description

IMP labelling requires unique identifiers to ensure traceability throughout the locations/areas and sufficient trial subject protection. At this stage, the label sample together with the packaging and labeling specifications are approved using a label release form for initial release to the site(s). In case of label changes, the release of an updated and reapproved label is necessary to ensure continuous supply.

5.6.2.2 Data and Risks Associated with the Process

The specification must include a unique identifier and essential information for the primary and secondary packaging components. The overall risk associated to this process is rated as high.

Defining the specifications for the label is a pre-condition for the labeling process. When a supplier is involved in the packaging and labeling process, procedures need to ensure that all involved persons at third parties are informed appropriately about the label status. Changes to the label specification may impact the master batch record (and the COC) and must be approved before packaging begins.

In general, labeling information may differ depending on factors like country-specific requirements, trial design, and language. GCP-related information on the labeling should include, but is not limited to:

I. General Information

- Statement that the IMP should be used for clinical studies only
- Statement that the IMP should be kept away from children (sometimes child resistant packaging is required)
- Sponsor's and CRO's company name, address, phone number as well as investigator's name
- Contact information for an emergency call when unblinding is required

II. IMP-Related Information

- Protocol number and, for submissions in the European Union, the EudraCT number
- Content of the package (e.g., product name, strength, batch number)
- Non-trial-specific product information (e.g., dosage form, weight, volume, or quantity)
- Storage conditions (and information if temperature monitoring is required)
- Expiry date and/or retest date
- Shipment address of the trial site, and possibly the third-party manufacturer
- Description of the primary packaging (e.g., bottle with induction seal caps or blister)

Further documentation should include:

- Start of the clinical study
- Trial design (e.g., double blind, single blind or open label) and if a comparator is used in the trial.

- The general randomization (code numbers) should be described and identified for every trial subject.
- Number of subjects receiving the IMP, placebo, or comparator. The code numbers for every subject should be traceable in case of an emergency.
- General Safety Data sheet
- Special precautions for the disposal of unused IMP
- Information about the return of the IMP (IMP Return Form)

The following points are potential risks:

- Incorrect blinding/packaging of correct medication. Accidental unblinding may affect the treatment, e.g., wrong code numbers sent to the recipient so that unblinding for emergency cases is not possible. Labels may also be missing essential information or may not correspond with their specified format (and may therefore not be in alignment with the specifications).
- Medication itself may unblind the trial due to specific features easily attributed to the related treatment.

5.6.2.3 Validation Approach and Challenges

Challenges include:

- Administration effort in connection with the variety and quantity of labels (versioning)
- Communication of changes to the affected (third) parties in a timely manner
- Re-labeling of the expiry date
- Changes in trial design

It should be thoroughly checked to determine if the medication complies with the randomization list.

Procedures for the visual label check should be established. Format, fonts, and size of the labels vary, which results in static and some variable areas where information differs between each label. As each label needs to be checked against the master label, (semi)automated visual checks may be helpful for quality control purposes. If systems are used for those checks, the intended use should be validated (including qualification of the equipment).

When using barcodes, controls should be established or the system used is to be capable of determining the readability and correctness of the printed code.

Quality agreements are always required when packaging is performed by a third party.

For managing packaging and labeling, an IRT system may be utilized, e.g., for processes that include features to support the enrollment, randomization, and to provide functions to track the IMP stock status for data input. In addition to the validation of this kind of system, appropriate data entry verification needs to be considered.

5.6.2.4 Typical Associated System Classes

Label checking systems are typically GAMP Category 3. Depending on the complexity of the labels the category may also be GAMP Category 4 or 5.

IRT system classes may range from GAMP Category 3 to 4 depending on the feature utilized within the clinical system.

5.6.3 Sub-process: IMP Shipment

5.6.3.1 Short Process Description

The shipping order of the IMP has to be approved, and the shipment organized and documented (shipping order/protocol) to ensure IMP distribution to the correct sites, as well as correct shipment to the sponsor in case of a return or recall.

For international studies with multiple sites, the IMP is typically shipped first to depots covering geographical areas and then in a second step, distributed to the participating clinical sites. During shipment, the IMP must be physically protected against damage and, where applicable, temperature and humidity controlled and monitored during the transport process (temperature logging).

Site-to-site transfers of IMP need to be authorized and documented, with country-specific requirements taken into consideration. This action is important, as essential documents have to be updated.

5.6.3.2 Data and Risks Associated with the Process

The overall process risk is rated as high.

The following shipment data should be available and correctly addressed:

- Subject Randomization List(s) for the related center for the clinical study
- Kit Randomization List(s)
- Packing documents for approval to be shipped to the related logistics partner
- Internal identification (e.g., barcode or RFID (Radio Frequency Identification) labels)
- Group responsible for shipment of IMP
- Group responsible for requesting shipment of IMP (e.g., clinical supply chain management)
- Specific shipping instructions for IMP

Potential risks include:

- Incorrect packaging information may result in IMP delivery to the wrong recipient or trial subject
- Delivery of the wrong randomization list may lead to the inability to reveal the code in an emergency
- Return/recall of an IMP resulting from critical temperature violations
- Frequent temperature violations and inappropriate length of IMP exposure to extreme environmental conditions may lead to a loss of product efficacy
- Loss of IMP during dispatch or due to a lack of security during storage
- Frequent temperature range violations during shipment may result in variances regarding efficacy within a batch and may therefore lead to different reactions of the trial subjects
- Delays may have a negative effect on progress and/or treatment of the trial subjects and could lead to protocol violations

5.6.3.3 Validation Approach and Challenges

It should be thoroughly assessed if the selected third-party provider has established an appropriate quality system to meet regulatory requirements and sponsor's business needs/requirements.

Depending on the mode of shipment and the sensitivity of the IMP, appropriate controls must be established by the provider in order to avoid any potential damage or loss of IMP and to assure the timely IMP arrival at the defined trial site.

Audits should be conducted to assure that the third-party provider implements appropriate controls. The provider should have procedures in place to demonstrate the ability to maintain temperature controls, manage changes, and conduct impact assessments in case of deviations from the defined ranges.

It is also recommended to confirm that the provider has a (secure) parking concept to prevent potential loss of IMP and a tested contingency plan to ensure, for example, safe dispatch of the IMP to another carrier, or handling issues with the temperature monitoring system.

Often a subcontractor is commissioned by the (primary) service provider. In these cases, the service provider must likewise establish a process to document that all quality requirements are met by the subcontractor.

In general, all temperature deviations should be taken into consideration (including length and frequency) in order to evaluate the efficacy of the IMP. Therefore, it is essential to use qualified systems (e.g., data logger) during shipment and storage to monitor temperature and to ensure integrity of the cold chain.

Data loggers should be recalibrated at regular intervals as defined in corporate procedures and, if connected to a computerized system (e.g., for report creation and sending), the system should be qualified. The process of sending temperature data from the receiving site to the batch release group needs also to maintain data integrity, e.g., by the use of proprietary, encrypted file formats.

The Mean Kinetic Temperature (MKT) should be determined to evaluate if the frequency and length of the temperature deviation may have an impact on product quality.

For highly sensitive IMPs it might be necessary to ensure traceability of location (e.g., per barcode) and storage conditions during shipment (e.g., correct orientation – upside/downside of the container) using GPS-based technologies.

If a supplier operates their own depots and is therefore responsible for environmental conditions, the supplier has to be qualified upfront based on the associated risks (e.g., via an audit). Computerized systems used by the supplier should be validated (e.g., environmental control including alarming and staff notification in case of a violation, security breaches, backup of electrical power, and logistics management systems).

For the IMP transfer, e.g., with trucks, only properly qualified refrigerated trucks or containers should be used. For transport modes where stable temperature conditions cannot be guaranteed or are too expensive, it is recommended to use qualified transport boxes equipped with battery-powered compressors (active cooling) and temperature loggers.

Staff should be trained on how to handle the IMP and when/how to escalate temperature violations or other unplanned events that could affect the scheduled timelines.

The challenge for these tracking technologies is the need for complete documentation and records over the entire supply chain to fulfill regulatory requirements (e.g., 21 CFR Part 11 [8]).

IRT systems may be used for IMP shipment, e.g., including features that provide functions to track the IMP stock status, alerts for upcoming expiry date updates, and recall using a telephone or the internet for the input of data. As mentioned in the chapter concerning packaging and labeling (Section 5.6.2), the validation of these systems and appropriate data entry verification should be considered.

5.6.3.4 Typical Associated System Classes

Monitoring systems, including MKT calculation, are typically classified as GAMP Category 3 or 4. Devices used for location tracking of the IMP are GAMP Category 3.

IRT system classes may range from GAMP Category 3 to 4 depending on the feature utilized within the clinical system.

5.6.4 Sub-process: IMP Accountability

5.6.4.1 Short Process Description

IMP use is limited to clinical studies and the sponsor is responsible for establishing controls in agreement with the site(s) to ensure this. Destruction of expired/excess IMP may take place at different locations according to written procedures, as the trial site might not always have the capability to destroy the IMP under controlled conditions.

Furthermore, destruction is only allowed if there are no unresolved issues. The outgo/return ratio should be used to calculate the needed IMP quantity so that a continuous supply is ensured for a clinical study. The drug-accountability documentation needs to be completed at the site and/or location where the process takes place, and a dated certificate or receipt concerning the destruction authorization/completion should be provided to the sponsor. The drug accountability documentation needs to be checked by the sponsor.

5.6.4.2 Data and Risks Associated with the Process

The risk of this process is rated as medium because there is no direct impact on patient safety or data integrity; however, without drug accountability processes, IMP use by the subjects cannot be properly reconstructed.

Data for destruction should be documented on the destruction form including a trace to batches and trial subject(s) as well as the quantity destroyed. The destruction form should be filed in the TMF.

Potential risks are:

- Insufficient IMP due to incorrect calculations
- Lack of IMP availability at critical times during the trial

5.6.4.3 Validation Approach and Challenges

The calculation system must be validated/qualified.

To prevent wrong calculations a drug accountability log has to be used. The destruction, controls for storage of unused products as well as the need for accounting and reconciliation should be described in SOPs. Distribution of responsibilities between sponsor and service providers should be defined and documented.

5.6.4.4 Typical Associated System Classes

The IVRS/IWRS system in use may include features that support enrollment, randomization, unblinding, and drug tracking. Depending on the trial, the system classes vary from GAMP Category 3 to 4. The same applies to data warehouse systems like SAP®.

5.6.5 Sub-process: Auxiliary Materials Management

5.6.5.1 Short Process Description

Auxiliaries are any trial-related items provided to the clinical sites additional to the IMP, e.g., syringes, test tubes, electronic diary devices, or latex gloves. Auxiliary material management encompasses the complete process, from purchase to the delivery at a clinical site, including stockpiling and logistics management. The ordering of auxiliaries should be documented.

5.6.5.2 Data and Risks Associated with the Process

The risk of this process is rated as medium because in most cases there is no direct impact on patient safety or data integrity; however, in some cases the risk may be considered low or even high, depending on the specific auxiliary material in question. For example, highly specialized materials needed for obtaining and preserving biological samples that might themselves require specific handling and shipment could be associated with a high risk, whereas standard tubes for drawing blood would not necessarily be associated with any significant risk.

One risk associated with auxiliary materials could be incorrect calculations of stock needed, leading to an undersupply to sites so that they are not available at the crucial time during the trial.

5.6.5.3 Validation Approach and Challenges

Any system used for the management of auxiliary materials for clinical trials should be validated/qualified.

To prevent incorrect calculations a log has to be used. Storage control and destruction of unused auxiliaries as well as the need for calculations should be described in SOPs. Responsibilities of service providers should be contractually delineated.

5.6.5.4 Typical Associated System Classes

IRT systems may include features that support auxiliary material management. Depending on the trial the system classes vary from GAMP Category 3 to 4. The same applies to data warehouse systems like SAP®.

5.7 Process: Subject Recruitment, Inclusion, and Randomization

5.7.1 Sub-process: Subject Inclusion and Informed Consent

5.7.1.1 Short Process Description

If a person volunteers to participate in a clinical study, he/she is informed about the trial design, objectives, conduct, risks, benefits, the participant's rights, and other aspects associated with the clinical study and must sign an informed consent as part of the subject inclusion process. After giving written informed consent and when it is clear the subject fulfills the inclusion criteria (and no exclusion criteria), the subject may commence treatment with the study drugs.

In emergency situations (e.g., trauma patients), consent can be given by other persons in accordance with national laws (e.g., by a legal representative). After the patient regains the ability to give consent (e.g., regains consciousness), he/she should also give his/her consent.

Once the number of subjects planned and defined in the study protocol (enrollment target) has been reached, recruitment has to be terminated. As a principle, subjects can withdraw their consent without stating the reasons at any time during the course of the study. All subjects need to be listed in the Subject Identification List of the site.

5.7.1.2 Data and Risks Associated with the Process

The data involved in this process is the subject data relevant for the inclusion/exclusion criteria. The signed Informed Consent Form (ICF) is an important study record.

Worldwide, the informed consent form is considered to be a legal document, and country-specific regulations apply. When considering electronic ways to obtain informed consent, country-specific regulations need to be taken into account. In Germany, for example, a qualified electronic signature according to the *Signaturgesetz* (SiG) [53] applies to any informed consent given, which makes electronic informed consent forms impractical.

The primary risks are that subjects are included in the study although they do not meet the study inclusion criteria, or that they are included without having given their informed consent. These are direct risks to subject safety; therefore, the risk associated is high.

5.7.1.3 Validation Approach and Challenges

Inclusion and exclusion criteria need to be defined in the study protocol and be implemented and validated in the eCRF used for subject recruitment.

It is still the practice in many studies that paper worksheets are filled out initially and data later transcribed into the EDC system; therefore, the inclusion/exclusion criteria need to be clearly checked on the primary worksheets.

In addition, the informed consent is usually signed “wet ink” on paper. Although any system could also ask the question whether (and when) the informed consent was signed and filed, such a check cannot be enforced on the system side but has to be performed by checking the paper document. The sponsor is not allowed to know the identity of the subjects, which also limits the possibility to check and enforce this in an EDC system.

During monitoring, cross checks and verifications are performed to ensure that inclusion/exclusion criteria have been respected and that the informed consents are in place. If it is seen during monitoring or by automated checks that a subject was enrolled in the study and given treatment mistakenly, such an incident is considered to be a protocol violation and corrective and preventive actions need to be taken.

5.7.1.4 Typical Associated System Classes

Inclusion/exclusion criteria checks and the check for the informed consent are typically configured or programmed for a trial-specific system, Layer III, GAMP Category 4 or 5; however, as described above, risk mitigation measures are mainly outside the computerized system (paper ICF checks, monitoring).

5.7.2 Sub-process: Randomization

5.7.2.1 Short Process Description

Randomization is the process of randomly allocating a subject number and treatment arm to participants. This process is based on a randomization list generated by the statistician. Depending on the study design, multiple randomizations are possible during the course of the study. Also, stratification may apply.

5.7.2.2 Data and Risks Associated with the Process

The main risk is that a subject is allocated to an incorrect treatment arm, either because of wrong stratification criteria or because of simple errors. There is an immediate risk to data quality, and a potential risk to subject safety; therefore, the risk associated with this process is high.

5.7.2.3 Validation Approach and Challenges

The stratification criteria and treatment arms need to be clearly defined in the study protocol and correctly implemented and validated in the trial-specific system. Additionally, the randomization list needs to be created in a validated process and protected against manipulation and unblinding.

5.7.2.4 Typical Associated System Classes

Systems used are trial-specific applications Layer III, which are either configured or programmed, i.e., GAMP Categories 4 or 5.

5.7.3 Sub-process: Emergency Unblinding

5.7.3.1 Short Process Description

In case blinded investigational products are used, the sponsor needs to establish a process of immediate unblinding, allowing the identification of the investigational product and, if necessary, the performance of a recall.

The investigator may perform unblinding in cases of a medical emergency. The identity of the investigational product may be disclosed to the investigator as far as required. Unblinding by the sponsor will be done only for relevant subjects.

The team responsible for pharmacovigilance on the sponsor's side (or a contracted service provider) also performs unblinding for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) to regulatory authorities.

Blinding should always be maintained as far as possible for all involved in the conduct and evaluation of a clinical trial.

5.7.3.2 Data and Risks Associated with the Process

Unblinding is performed in situations when subject safety is at risk. The unblinding has to occur quickly and correctly; therefore, the risk associated with this process is high.

5.7.3.3 Validation Approach and Challenges

Systems used for emergency unblinding must be validated and consistently available.

Special consideration needs to be given to user roles and user management and the sending of automatic unblinding notifications, so that these are only received by the personnel that actually need to be unblinded. These notifications should only contain exactly the unblinding information needed. Sealed envelopes distributed to the sites can be a workaround if computerized systems fail.

5.7.3.4 Typical Associated System Classes

Often, emergency unblinding is a functionality in a system that supports other processes. In most cases, these are trial-specific applications, Layer III and are configured or programmed, thus GAMP Category 4 or 5.

5.7.4 Sub-process: Data Collection, Entry, and Review (site)

5.7.4.1 Short Process Description

The data collected in a clinical study will be documented in the eCRF and signed by authorized staff. All changes or corrections, including self-evident corrections, need to be confirmed and signed by the investigator.

Data entry into the eCRF starts with the subject recruitment phase and is maintained throughout the study. This data entry is done on site either on paper or directly within an EDC system. The clinical monitor and possibly the data manager continuously review the data entered either onsite or remotely and data verification is conducted where needed in cooperation with the investigator. Also, the monitor performs the source data verification, and the site is monitored for regulatory compliance.

Additionally, the investigator records AE and performs emergency unblinding when required to protect the subject's safety. Once the data from all sites and subjects has been collected and reviewed and all queries clarified (including data transferred from central laboratories), the database is locked.

5.7.4.2 Data and Risks Associated with the Process

A potential risk is data entry by an unauthorized person. The system needs stable user and access rights/authorization management and an audit trail to trace the entries. The data entry of source data in the EDC system has a direct impact on data integrity; therefore, the risk is high.

To mitigate this risk, data entry checks implemented in EDC systems can give an alert directly during the data entry process and avoid the collection of implausible data (e.g., checks on the correct data format/type of entries, whether visit dates or dates of investigations are in a plausible range).

Furthermore, there are several downstream processes for checking the data correctness, e.g., source data verification by the monitor (the extent of SDV activities are typically defined in the monitoring plan) and data review by the data manager/reviewer/medical expert as a quality control function. Double data entry to discover erroneous data is a quality check if paper-based CRFs are transcribed to the eCRF.

Training of data entry staff and high diligence are important to ensure that source data will be correctly documented at the site. Also, independent audits should be performed to check and confirm the correctness of data and compliance with the protocol, SOPs, GCP, and applicable regulatory requirements.

5.7.4.3 Validation Approach and Challenges

The trial-specific part of the systems must be validated and the accurate processing of entered data must be assured (data entry and data storage).

5.7.4.4 Typical Associated System Classes

Systems used are trial-specific applications, Layer III, which are either configured or custom programmed, thus GAMP Categories 4 or 5.

5.7.5 Sub-process: End of Recruitment

5.7.5.1 Short Process Description

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Once the required number of subjects has been reached, the enrollment of subjects will be closed. The subject identification list will be locked and archived as part of the ISF.

5.7.5.2 Data and Risks Associated with the Process

Sites must be informed if the scheduled number of subjects has been enrolled; therefore, efficient communication processes have to be in place. Otherwise more subjects would be recruited than defined in the study protocol and covered by subject insurance. Also, a lack of sufficient IMP could also lead to subjects not being treated. This holds a high risk on subject safety.

5.7.5.3 Validation Approach and Challenges

In case systems are used to support the management of the end of recruitment, the special functionalities, e.g., for giving an alert to the user or closing the recruitment phase (such as preventing documentation of new subjects in the system) have to be accurately validated.

5.7.5.4 Typical Associated System Classes

Systems used are trial-specific applications, Layer III, which are either configured or programmed, thus GAMP Category 4 or 5.

5.8 Process: Data Aggregation and Review

5.8.1 Sub-process: Central Data Collection and Storage

5.8.1.1 Short Process Description

The collected study data is transferred to the sponsor for consolidation and statistical analysis. This includes the data entered into the eCRFs, the assessment and reporting of AEs, administrative data such as sample data (sample labels), laboratory management data, subject diaries, medical device data, and more. Pharmaceutical technical complaints can also be managed by the central database.

In this context, two aspects should be considered: first, the central storage of the study-specific data at the sponsor/CRO and, second, the central storage of all data gathered from different studies in the sponsor's clinical database. The validation focus lies on ensuring correct data entry (input), data storage, and data display and retrieval (output).

Interfaces between the database of an EDC system and the databases of laboratory systems are possible (automatic or manual). In this case, all study-relevant laboratory data is transferred and stored in the EDC database of the clinical study, resulting in central data storage.

The study database is set up using a given database structure (e.g., CDISC CDASH as the "gold standard") or, if a non-standardized database structure or supplier-specific standard is used, the study data is usually transferred into the Study Data Tabulation Model (SDTM) standard for transmission to the sponsor (data owner) for further analysis and storage. Regulatory authorities (FDA, EMA) request that they receive the study's raw data in SDTM standard [54, 55].

5.8.1.2 Data and Risks Associated with the Process

Clinical study and subject data are directly concerned and involved in this process; therefore, the risk is high.

If an EDC system is used and data is entered manually into the eCRF, there is a risk of typographical errors or mixing up data at the site. For example, instead of entering the visit date in the eCRF, the date of data entry could be entered, or data of the wrong subject could be entered. Comprehensive training of system users, SDV processes, and smart EDC systems can minimize the risk.

Potential risks associated with system functionality might be the incorrect storage of entered data in the EDC system, the inaccurate display of data, deficient data calculations or data exports to other systems.

If relevant data is not stored in the EDC system (e.g., from central laboratories, central image readers, or central ECGs), then additional risks arise from the decentralized data storage in those systems. These then also need to be validated (see Section 6.5).

5.8.1.3 Validation Approach and Challenges

Ensuring the integrity of the data entered via an EDC system and stored in the database is the main focus of validation. Validation must cover all essential steps of the data collection process: data entry, storage, retrieval/display, and calculations. Additionally, interfaces to other systems and to the sponsor's database must be validated.

The validation approach is two-fold:

- Validation of the EDC system
- Testing the study built with the EDC system against the specifications of the protocol.

To reduce the risk of typographical errors or mixing up data during data entry, it is normally sufficient to provide adequate training, which is the responsibility of the sponsor/system owner.

No user should have access to the system without at least basic training. Different types of training are possible, reflecting the diverse levels of complexity of the various systems, the role of the user in the clinical study, the experience of the individual users and, last but not least, the time the user is willing to spend on the training. Training options include instructor-led face-to-face training, web-based training, training via telephone, or self-paced online eLearning courses.

Training is usually done as part of the site initiation. For users who do not take part at that time, web-based self-training is considered the bare minimum.

The training of site users, for example, should cover:

- General functionalities of the system (data entry and saving, navigation)
- CRF completion guideline and a support hotline
- CRF structure and time frame of visits
- AE/SAE reporting including timelines
- Signature of the CRF pages/data
- Query management

Another challenge for data entry at the site is that it is often done alongside daily business. This potential risk for quality issues should be evaluated during the site evaluation/selection process.

Other risks concerning data entry (such as the scenario involving the insertion of the date of data entry instead of the visit date) can be mitigated, but not completely eliminated, with smart plausibility checks and alerts within the EDC system according to a Data Validation Plan.

The validation process to ensure correct system functionalities (data storage, data retrieval/display, calculations) consists of testing the system against clear specifications according to detailed test plans and test scripts, and following a detailed risk analysis as described in the *ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Testing of GxP Systems* [55].

5.8.1.4 Typical Associated System Classes

Training systems or LMS, is usually GAMP Category 4.

The EDC system consisting of a Graphical User Interface (GUI) and the relation to the underlying database is usually GAMP Category 4 or 5.

The clinical database itself, if set up using an appropriate and validated standard format (CDISC), could be classified as GAMP Category 3, if it is not customized or configured at all.

5.8.2 Sub-process: Blinded Reading/Independent Image Review (in imaging studies)

5.8.2.1 Short Process Description

Blinded Reading (BR) is an objective method of analysis for imaging data collected in clinical studies. The focus of activities is the image management process and, if applicable, the blinded assessment of images by independent experts. An imaging charter aligned to the study protocol should be in place.

In clinical studies dealing with, e.g., diagnostic procedures or oncological therapies, the reading and evaluation of images is an essential part of a study's design and the results of these readings are very often critical study endpoints.

The reading and interpretation of images, however, is highly dependent on the person reading the image because the ability to do this reading correctly depends greatly on the person's experience and training.

Even when the required expertise is present, the nature of reading and interpreting images remains a process with inherent imprecision. As a result, there is often a need to have a second opinion on a particular image's evaluation. This can be managed by using Independent Image Review (IIR), where the same image is reviewed by a second independent reviewer and the results of the review are compared.

For example, in a study in which the therapy with the IMP is only allowed for subjects with inoperable tumors, a second opinion and an agreement about the diagnosis can help to minimize the risk of the subject receiving the wrong treatment and can avoid a decision for or against the study therapy based on other inadmissible factors.

In another example, when a study endpoint concerns tumor response to a certain therapy by measuring changes in a set of standardized evaluation criteria (e.g., RECIST criteria), it is essential that the criteria evaluated in the images are interpreted correctly; here too, a second opinion helps objectify the readings.

Procuring a second opinion may not only help to arrive at a correct evaluation of imaging studies as a basis for therapy decisions: the reading process itself may be the topic of a trial with the objective to compare differences between results with the ultimate aim of developing new diagnostic algorithms, or for appraisal defining guidelines to reduce variability and uncertainty in image interpretation.

For these purposes, it is necessary to ensure that the image readings are truly independent and blinded. The person performing evaluation of an imaging study should be blinded to:

- Information on the subject or study that may influence his or her reading of the image
- The results of other readings of the same image to preserve their objectivity.

By providing for two independent readings of the same image and then reconciling the results of those readings, the likelihood of an accurate interpretation of the image increases, and the conclusions drawn from this process are more apt to be valid.

5.8.2.2 Data and Risks Associated with the Process

The data in this process can range from single pictures of, e.g., skin lesions/abnormalities, or radiological procedures, to Digital Imaging and Communications in Medicine (DICOM) data sets from MRI/MRA assessments, or even film material of ultrasound or endoscopic sessions. The processing system needs to manage this variety of data in a way similar to any other data (i.e., saved, displayed, calculated), but imaging data is particularly complex.

While data stored in a database usually is entered in a field, stored as a defined field type (e.g., varchar) in a database, and used for calculations in simple algorithms together with data from other fields or other variables, the data used in a blinded-reading process can be a challenge even for storage.

The expected data characteristics, such as data format and size, need to be well known. Adequate storage of this data can be complex and may require large amounts of space (e.g., 2 GB per subject), in addition to a dedicated server.

Depending on required functionalities, a separate system (distinct from an EDC system) may be necessary for distributing, displaying, annotating, and storing images. Displaying these pictures often requires special program components that go beyond the scope of GCP relevant systems and need to be certified as medical devices in case they are used as tools for diagnostic evaluations.

Because the review of these images is to be independent and blinded, systems that handle this information must provide for the possibility of distributing the same images to multiple assessors in a blinded fashion, i.e., without revealing either the annotations or results of the previous reviewer, or blinded-subject information. Nevertheless, this information must be retained in the system to allow correct matching of an image with the subject and to facilitate comparison of the results of the two or more independent readings.

The risks associated with this process are incorrect or poor-quality storage of the image data and incorrect mapping to the subject.

In addition, there are specific risks to subject privacy and to maintaining the blind when personal subject information is retained in the system. Often the data comes from hospitals' Picture Archiving and Communication Systems (PACSSs) and needs to be anonymized when transferred (manually or electronically) to the system used in the study (picture archiving and communication systems).

When images are displayed, no single pixel is allowed to be lost; therefore, special hardware such as high-resolution screens is needed.

Depending on the trial design and endpoints, the impact of imaging data on subject safety and the validity of a clinical study can be significant.

5.8.2.3 Validation Approach and Challenges

As the risk associated with the human factor in image evaluation and interpretation cannot be easily reduced in this process, it is of particular importance to start the validation of systems used in the BR process with qualification and training of the sites and "blinded readers".

Specialized hardware is required for displaying and reading the images, e.g., medical high-resolution screens. This hardware and specialized software for displaying the data are subject to the regulations of medical devices and must be certified according to these standards.

When determining the best approach to validating GCP-relevant systems involved in BR, it may be useful to consider the flow of data through such systems. The original imaging data is part of the TMF, and therefore has to be stored in a database. This database requires validation to address the aforementioned risks to ensure correct storage, retrieval, and display of the images, as well as correct mapping to subjects.

In addition, functions that serve to maintain the blind and the independence of the image reviewers are of particular interest.

The image data itself is then supplemented with data resulting from the reading (e.g., the report on the findings and their interpretation). This data may be captured in the same system that handles the images or it may be entered into a different one. The system capturing the results would need to be validated like any EDC system with functional testing and testing to ensure correct storage of data in a database.

Of note, systems used in this process are not only GCP-relevant, but overlap with medical device and data privacy regulations and laws.

5.8.2.4 Typical Associated System Classes

As mentioned before, systems used for the display of image data need to be highly adapted to the data type and study objective, therefore, mainly custom-built systems of the Category 5 or highly configurable Category 4 systems are in use.

For automated exchange of DICOM data with EDC systems, interfaces between PACSs and EDC systems can be implemented.

5.8.3 Sub-process: Monitoring

5.8.3.1 Short Process Description

Clinical monitors (Clinical Research Associates (CRAs)) keep the sites under surveillance with respect to correct conduct and documentation of clinical studies. The checking of all recorded data for completeness and correctness takes place via remote monitoring through the EDC system as well as SDV onsite.

The type (onsite versus remote) and extent of monitoring, as well as the data points to be verified, must be clearly defined in the monitoring plan.

In August 2013, the FDA published its final guidance on Risk-Based Monitoring (RBM) [56] encouraging the pharmaceutical industry to implement a risk-based approach to monitoring, moving from routine site visits with 100% SDV to a more targeted approach.

As the EMA endorses an equivalent approach in its “Reflection paper on risk-based quality management in clinical studies” (November 2013) [57], following a risk-based approach to develop the monitoring plan is recommended. This approach focuses on the critical study elements/data points needed to investigate the trial objectives.

The type and extent of monitoring depends, among other parameters, on the study phase and its design. Monitoring activities range from 100% monitoring of all data points (e.g., Phase I study) to monitoring of defined key data for all or certain randomly-selected subjects. Any discrepancies are resolved by queries to sites and traced with the query management process within the EDC system.

Compliance with the study protocol and regulatory requirements, as well as drug inventory and general support and training for the site staff, are the focus of on-site visits (site compliance check). All monitoring activities and action items are documented in the monitoring visit report and the follow up letter to the site.

The close out visit takes place after termination of the clinical study and completion of all activities at the site.

5.8.3.2 Data and Risks Associated with the Process

Training plays an important role in overcoming objections and outlining capabilities and benefits of RBM.

It is important to take into account the interactions between the various players like the sponsor, CROs, laboratories, EDC vendors, and to define responsibilities, lines of communication, escalation procedures, and so on.

With risk-based monitoring, the role of monitors will change. The monitors will have to be better trained in technology than before, and will need sound functional, operational, and regulatory expertise to identify and analyze risks.

Excellent communication skills will become even more important in order to manage sites remotely and to communicate any issues internally to decision makers.

Last but not least, the monitors will have to show a higher degree of flexibility to respond to the changing monitoring needs that arise throughout the study life cycle.

RBM will also change the role of the project manager, who will have to live risk-based thinking and take over a crucial part in assessing risks and coordinating the necessary adjustments and activities.

RBM implies careful consideration of both on-site and remote activities. On-site visits will not totally disappear. Besides study initiation and close out visits, there will always be monitoring activities that cannot be performed remotely. Reviewing subject charts is a method to detect additional safety information, which may not emerge through pure SDV.

There are other issues that can only be detected on site (e.g., problems with drug storage), and some issues will only be brought to the sponsor's attention because of the good relationship between monitor and site (e.g., upcoming resource conflicts).

With the increasing use of technology and the possible reduction in monitoring visits to well-performing sites, the relationship between monitor and site becomes even more important.

Also, a RBM approach has to consider that risk analyses, subject profiling, and trend analyses are only feasible if data is available: the more data available, the more precise the results of the analyses will be. Pure automatic detection of outliers may only be of limited use and certainly requires additional medical assessment to trigger further activities or not.

Finally, the balance between on-site and remote monitoring should be adapted to the special needs of a trial. For example, it may be decided that is necessary to perform 100% SDV when monitoring an early phase study.

For remote monitoring, data confidentiality aspects need to be considered for the data transfer between site and monitor.

5.8.3.3 Validation Approach and Challenges

EDC systems can support monitoring activities by using alert functions for checking empty fields or logically incorrect data points. This facilitates visual data verification and allows the monitor to focus on SDV on site.

Modern EDC systems also support RBM on various levels (data, site, study, and program) and allow graphical presentation of data for sophisticated analysis.

Monitoring activities are scheduled in the monitoring plan; it is recommended to follow a risk-based approach for its creation.

Furthermore, involved clinical monitors need to be trained on the study protocol, monitoring plan, and the functionalities of the EDC system including RBM and automatic checks performed by the EDC systems, so that the resources of monitors can be allocated most effectively.

The increase in application of the RBM approach has been supported by the fast development of technology in recent years, which enables continuous surveillance and real-time access to data. Electronic collection and integration of data from various sources (e.g., EDC, CTMS, ePRO, Interactive Voice/Web Response System (IxRS), laboratories) provide more transparency and a more holistic view on data. Tools for sophisticated statistical analyses, visualization of results and trends through dashboards, interactive reports, and automatic alerts based on metrics allow a more strategic approach to monitoring.

RBM should be embedded in an overall Risk-Based Quality Management strategy. Planning should start early in the study life cycle and bring all involved parties together, such as project managers, therapeutic experts, quality assurance, data managers, biostatisticians, pharmacovigilance experts, and monitors, including third parties, sites and vendors, if necessary.

The risk-based approach is based upon defining key data and key processes and their corresponding key risk indicators, allowing efforts to be focused on these critical items. While errors cannot be entirely avoided, the important question is whether these mistakes could influence the key objectives of the trial.

The traditional monitoring approach is more reactive; monitors and data managers reacted to mistakes that were identified on site. Now, with new technologies, there is the possibility to detect risks and quality issues early and react proactively in a specific, targeted way and thus use resources where they are needed most.

The goal is to identify risks early and initiate appropriate corrective actions.

Possible risks, thresholds, and remediation activities as well as the time point and frequency of control and remediation actions have to be described in the monitoring plan. The risks should be assigned a risk level (for example high, medium, low) or a threshold (such as x% higher than baseline). For instance, if one site has significantly more queries than others, possible actions could be more frequent monitoring visits, additional training, changes in inclusion/exclusion criteria (mid-study change), or assigning more/other people to the trial at the study site.

Quality parameters and risks should be described and surveyed on all levels, for example:

- Study level: study phase, indication, drug, vulnerability of subject group, historical data of similar studies
- Site level: experience of site personnel, drug accountability control measures
- Data level: error rate, protocol violations
- Resource level: CRA experience with RBM, EDC, sites, knowledge of cultural aspects, communication skills

Controls and resulting actions need to be documented (who, what, when, why). This includes re-adjusting thresholds and triggers, if needed.

Since technologies play a key role in enabling RBM and decisions are based on their output, it is important to ensure that the data is accurate, robust, and reliable. Since most of the systems are no longer stand-alone implementations but building blocks of an integrated eClinical Platform, it is important to validate not only the individual systems, but also the integration and flow of data through the various systems. The transfer from one system to another must work correctly and data must not be misinterpreted.

A backup solution and business continuity plan are also needed in case one of the systems is not available.

5.8.3.4 Typical Associated System Classes

Typically, EDC systems support the data review process (monitoring and data management activities). A big part of alerts/checks can be programmed in a standardized fashion within the core functionality of the system (e.g., checking for empty fields or logically incorrect data), so they can be assessed as systems of GAMP Category 3 or 4.

All study-specific checks need to be validated like GAMP Category 5 systems (refer also to Section 5.3).

The number of available systems to support RBM has radically increased in recent years. These systems range from simple reporting within the EDC system, or connected CTMS, to completely separate systems using the EDC data for complex data analyses. Since the critical values/key risk factors need to be re-defined for each study, these systems will generally be classified as Category 5 or at least Category 4.

5.8.4 Sub-process: Data Management

5.8.4.1 Short Process Description

Data management in clinical studies is a defined process and must not be confused with the understanding of data management in the IT field. In the context of clinical studies, data management describes the checks on the data regarding completeness and plausibility; whereas in the IT field, this is understood as the details of the logistics of data storage and handling.

In clinical studies, data management processes constitute the foundation of study data validation and integrity. Therefore, the data manager is involved in/responsible for eCRF development, database and EDC set up, data cleaning (query process), and all activities to prepare for database closure.

It is common to split these responsibilities into the technical and systems-related part (EDC set up and validation) and the data reviewing part (definition of CRF, edit checks, and data review and cleaning including query management).

All data management activities in a clinical trial are precisely described in the associated data management plan, which includes or references a data verification plan.

After completed monitoring visits, or at defined time points (e.g., when all subjects have finished treatment or when an interim analysis is planned), trial data managers perform data quality checks according to the data verification plan. If discrepancies in the clinical database are identified, an extended query process is used, ultimately aiming to achieve high quality and valid trial data.

5.8.4.2 Data and Risks Associated with the Process

As mentioned, in current practice, the data management tasks are usually split into the more EDC-related and the data-related parts. The EDC part is dealt with in Section 5.3. The data-related part is the focus here.

Due to the fact that all checks by data reviewers are done retrospectively, they have no direct impact on subject safety and are therefore of medium risk for subject safety.

However, because data managers might be able to change data, the risk to data integrity is high. The risk-minimizing actions in this process are subsequently done by a three-step method.

The first step in the data management process, and at the same time the first risk-minimizing action, is to create a data validation plan, which defines the checks to be performed on the data, as part of the overall data management plan. Several groups working on the clinical study should provide their input on these documents (including medical staff, project managers, and statisticians) to determine the validation checks on the basis of the study objectives and expert knowledge.

According to the data validation plan, the second risk-minimizing action can be performed. For this step, the data checks need to be evaluated as to whether or not they will be implemented as automated alerts in the EDC system (direct checks of data for plausibility during data entry), or whether they will be done manually later by checking data listings. On the basis of these decisions the monitoring plan can be developed with the details of SDV and plausibility.

As a result, the data manager only needs to perform the non-automated checks that remain (which is the third step) and can therefore concentrate on these mostly medical checks or complex crosschecks requiring expert knowledge that cannot be automated. The risk here is again the human factor, which per se includes an error rate. It can be minimized by thorough training and experience of the data managers.

5.8.4.3 Validation Approach and Challenges

Often Query Management Systems are deployed in which the queries themselves, the answers, and the status of the queries (open, answered, accepted/closed) can be stored and reviewed.

It is possible that the query management system is embedded into the EDC system, or the information might only be collected in simple lists. The documented and signed answer by the investigator, either with direct changes and re-signing of the data or via an electronic Data Clarification Form (DCF), is important for this process.

The queries are created based on manual review of the eCRFs, data listings implemented as automated report functions in the EDC or CTMS, or as manual Structured Query Language (SQL) queries performed on the study database itself. Also, a Statistical Analysis System (SAS) is commonly used to perform edit checks on the clinical database and report discrepant data to the data manager.

In case an EDC- or CTMS-embedded system is used, the validation of this query database is part of the validation of these systems with testing of all the related functions (including storage and display of entered data), as well as testing of special functionalities.

The validation approach for the data listings is, firstly, the definition of requirements and rules (which data need to be shown in the listing), and secondly, testing if the database query implemented delivers the right data set.

The design of the user roles and user account management is important to mitigate the risk of unauthorized data changes.

5.8.4.4 Typical Associated System Classes

Typical associated system classes to this process and its various steps are the same as for EDC systems with implemented automated alerts. The GAMP categories for EDC are described in Chapter 5.3 Process: EDC System Life Cycle and Validation.

In case the EDC systems and CTMS are used as a platform to create the listings, the implementation of such a reporting function might constitute a configuration to the system, which is then Category 4; but if the listing itself is highly customized, testing of query results has to be done on customized test plans and is Category 5.

Even in the case that such listings are done manually by typing the SQL or SAS query without using a dedicated system, the query and its result have to be validated as a Category 5 system.

5.8.5 Sub-process: Medical Coding

5.8.5.1 Short Process Description

Especially in global trials with clinical research staff from various countries, standardized data entry is a challenge and medical data might be recorded in different ways.

This is particularly true for medical terms like medical history, concomitant medication, and AEs; therefore, medical coders are categorizing clinical terms according to certain dictionaries, so the data entries are standardized for further analysis and reporting to authorities.

Medical coding of data is necessary if records are created as free text entries. This must be done before data is merged and used for statistical analysis. The coding is performed with the aid of standardized classification systems. The most popular coding dictionaries are the WHO Drug Dictionary [58] and MedDRA [46]. Also common are the International Classification of Diseases (ICD) [59] and COSTART [60].

There are coding systems available that provide versioned standardized classification lists; these systems can be used for searching terms and selecting codes. In some cases, the systems (e.g., the MSSO's MedDRA Browser [46]) are separate applications run on local workstations. In other cases, EDC systems include integrated coding tools as a feature.

Typically, recorded causes of death, diseases, AEs, and procedures (subject history data, concomitant medications) have to be coded in the appropriate coding system.

Some data is always coded because of regulatory requirements. For example, many of the fields containing information to be reported within an electronic SUSAR report to an authority are coded according to systems and lists defined by the ICH and ISO. While in some cases this coding may be restricted only to the pharmacovigilance database for the trial, usually there will be an impact on the clinical study database as well.

Coding is a manual process performed with the help of or based on standardized coding lists that result in reference tables consisting of the recorded verbatim term and the reference code.

For some coding systems (including MedDRA [46]), translation modules for various languages are available, although some of the lesser-used language modules often contain a significant number of errors and should be reviewed carefully before use.

The reference tables are used for further statistical analyses.

A review of medical coding by a medical expert is absolutely necessary and ensures the correctness of the medical coding process. Before coding can be performed for a live study, the coding functionality needs to be tested.

The medical coding dictionary has to be connected to the eCRF and verified that the correct codes are assigned to the medical terms. It should also be checked that the correct version of the dictionary is used and that licenses have been obtained.

For example, MedDRA [46] releases two versions per year with updates and changes. It needs to be considered thoroughly whether a dictionary should be updated during the course of a trial, or if the same version will be kept for the length of the trial. As this requires a review of updates to the codes with each new release, along with a reconciliation process to decide how to handle the changes in codes both retrospectively and prospectively, it is common practice to define a specific version of the coding system for a clinical study and maintain all codes in that version for the duration of the trial.

It should be noted, however, that when electronic reporting requirements for a SUSAR report require a current version of the codes to be used, re-coding in some form is inevitable and must be subject to a controlled process. It is recommended to perform coding on cleaned data.

In the eCRF coding of terms can be performed automatically, e.g., if there is a 100% match between the term in the eCRF and the term in the dictionary (auto-coding). It is a decision of the study team as to whether the code should be displayed in the eCRF or hidden from the site staff.

For terms that fail auto-coding, the medical coder manually selects the correct term from the list available in the dictionary. Typically, this is performed by medical experts. It is important that the medical coders have read access to the entire eCRF, so that the term to be coded is in the correct medical context. Often, there is further approval of all terms additional to the coding process as a final step.

5.8.5.2 Data and Risks Associated with the Process

The first risk is that the software solution is not implemented correctly and problems arise during the coding process. Thorough validation and user acceptance testing before the system goes live can avoid this risk.

It is not always possible to code eCRF entries right away and queries to the site are needed. Typical problems that can arise during coding are spelling mistakes, use of abbreviations, incomplete information, recording of symptoms instead of diseases, recording more than one term in one entry field, and recording of local brand names.

Incorrect coding could have an impact on statistical analyses, but the source data is available at any time; therefore, the risk is medium to low.

Appointing trained and skilled subject matter experts to the coding activities, using standardized coding lists (in the current or at least consistent version), review/approval of medical coding, and reconciliation with the sponsor's database are measures to ensure the accuracy of the process.

5.8.5.3 Validation Approach and Challenges

Validation of the relevant computer systems has to occur before going live. This effort needs to include the interface between the eCRF and the coding dictionary. Validation should also incorporate user acceptance testing by the medical coders focusing on the process and practicability of the solution.

If a new version of a dictionary is implemented, additional and appropriate validation is required.

Medical coding helps to classify and categorize AEs, diseases, and medications. The source data is not changed and remains available for verification at all times. The coding results should be checked by a second review because medical expert knowledge is required.

The result of the coding process is a reference table between verbatim terms and the standardized code.

5.8.5.4 Typical Associated System Classes

Systems used for coding and storage of dedicated codes range from GAMP Category 4 to 5.

5.8.6 Sub-process: Database Lock

5.8.6.1 Short Process Description

Data cleaning, the prerequisite for locking the database, comprises the check that:

- All eCRFs exist and have been signed off
- All queries of the responsible clinical monitor and the data manager have been resolved
- The coding process has been completed
- Reconciliation of SAEs is complete

In case of double data entry, the final reconciliation process must be performed.

Depending on the organization, locking the database can occur in different stages, often called soft lock, hard lock, interim lock, or final lock. The final lock of the database contains the final status of data for the final statistical analyses.

5.8.6.2 Data and Risks Associated with the Process

Database lock is the process to finalize study data and keep it safe for statistical analyses. After database lock, study data should no longer be changed.

If changes or corrections of data become necessary after the lock, a controlled process must be in place for unlocking and relocking the database that needs to be described in SOPs.

There are two risks associated with this process. First, there is the possibility that the data cleaning process has not been completed when the database lock takes place. Second, data might continue to be modifiable; therefore, the risk to data integrity is medium, while there is no risk to subject safety.

5.8.6.3 Validation Approach and Challenges

Database lock is the final step of data management activities defined in SOPs and the Data Management Plan (DMP), and involves closing the database. After this, the data is ready for statistical analyses.

It is recommended to use a checklist for database closure to ensure that all queries have been resolved, all data management activities have been completed, and all signatures have been provided.

5.8.6.4 Typical Associated System Classes

Database lock, as a function of an EDC system, inhibits writing access to the system for all roles. This part of an EDC system needs to be validated as a GAMP Category 4 or Category 5 system.

5.9 Process: Severe Adverse Event Reporting

5.9.1 Sub-process: Severe Adverse Event Recording and Reporting

5.9.1.1 Short Process Description

In order to maximize subject safety during a clinical study, it is essential to record and analyze all serious and non-serious adverse events. AEs are considered serious when they fulfill certain regulatory criteria (see Glossary). A subset of these Severe Adverse Events (SAEs), in turn, qualifies for expedited reporting by the trial's sponsor to regulatory authorities and ethics committees.

Generally speaking, there are three distinct reporting lines for managing this important safety information:

1. The information on SAEs must be documented and reported by the investigator to the sponsor (or sponsor's representative, such as a CRO).
2. The information received from the investigator is recorded, processed, and triaged for reportability by the sponsor or CRO, and then reported, as appropriate, to regulatory authorities and ethics committees.
3. Information is looped back to the investigator concerning reports submitted to regulatory authorities and ethics committees.

For each of these reporting lines, different reporting criteria, timelines, and content are applicable.

When an investigator observes an SAE, the investigator is obligated to report it to the sponsor immediately, usually within 24 hours. This reporting activity is independent of whether or not the investigator believes there is a causal relationship to a medicinal product.

The reporting process is often performed via email or fax, and the SAE is also captured (along with all other non-serious adverse events) in the eCRF.

It should be noted that it is common to have follow up reports on an SAE because the reporting requirements are such that relevant information not available at the time of the initial report needs to be sent. As an SAE can be an event of some duration, it is likely that many follow up reports will be tied to a single SAE.

It is possible to exclude certain SAEs from immediate reporting by the investigator per study protocol (e.g., planned hospitalization, trial endpoints).

Upon receipt from the investigator, the sponsor or the CRO records the SAE information, usually in a separate safety database or database module.

The (re)assessment of the SAEs for seriousness, expectedness, causality (a necessary criterion for reporting), completeness, and reportability is customarily performed by a specialized team that is distinct from the team performing analyses of trial data to ensure that individual data does not result in a bias for these analyses. When a report appears to be incomplete or there are inconsistencies in the data, the investigator is contacted to provide clarification.

When individual SAEs are identified as reportable SUSARs, they are reported within the legally stipulated time frames (7 or 15 days) to regulatory authorities and ethics committees.

Reporting most often takes place in a standardized electronic format (e.g., an ICH E2B(R3) XML file [61, 62]) through reporting systems set up by regulatory authorities, but reporting may also be done via fax, email, or paper, depending on the requirements of the recipient.

The SAEs collected for a trial are included in annual reports (Annual Safety Reports, DSURs, IND, or NDA reports) and in the final Clinical Study Report (CSR) submitted at the end of the trial, subject to regulatory requirements applicable for the addressee.

Finally, SAE management also includes the continuous communication to the investigators about potential safety issues (information on SUSARs and changes in the safety profile).

As there is usually a separate pharmacovigilance database to collect safety data, it is necessary to perform reconciliation between the pharmacovigilance database and the data management system to ensure data integrity.

5.9.1.2 Data and Risks Associated with the Process

The safety processes potentially have a direct impact on the safety of the subject. Timely processing and reporting to the relevant recipients of the SAE data ensures that the safety profile of the investigational medicinal product is constantly monitored and that appropriate actions can be initiated if the safety of the subjects participating in the trial is at risk.

Because the source of the data on SAEs is the investigator site, any issues arising at the site level leading to delayed reporting of SAEs to the sponsor, or even omission of reporting SAEs, constitute risks to regulatory compliance and to the overall safety of the trial participants.

However, even when reporting from the investigator to the sponsor is timely, issues concerning content can still pose a challenge. Every SAE report must contain information on at least an identifiable subject, an identifiable reporter, an AE/reaction and an identifiable medicinal product. Nevertheless, these minimal criteria serve only to start the clock for reporting timelines.

The expectations for the quality of the reports are much higher, for the reports must contain all relevant information necessary for the correct assessment. Particularly the assessment of aspects such as cause and expectedness require detailed information on the event in question, including information on other factors that may have contributed to the event.

Since an accurate assessment is critical for interpreting the impact of an SAE report, there is an inherent risk associated with incomplete or inaccurate data provided by the investigator. If critical data is missing from the report or the data is inconsistent, every effort has to be made on the part of the sponsor to quickly get the necessary clarification from the investigator.

In reporting of SUSARs to regulatory authorities and ethics committees, the compliance with regulatory timelines and content is dependent on the correct functioning of the supporting electronic systems.

In addition, from a process perspective, reporting requirements to regulatory authorities and ethics committees can vary internationally, so it can be a challenge to adhere to different requirements and to stay up-to-date as to what those requirements are. When regulators and standards organizations issue new technical standards for reporting (e.g., the HL7® initiative [63], new ISO Individual Case Study Report (ICSR) Standard [64], etc.), this poses the risk of a technical disruption of the reporting process and may result in non-compliance if not addressed.

In processing SAE reports, the risk of unblinding must also be managed, as it is essential that persons directly involved in the conduct of the trial or its analysis remain blinded to the treatment allocation of the subject. For example, when information on SUSARs from an ongoing blinded trial is communicated to the investigators, it is essential that the investigators remain blinded when they receive this information from the sponsor.

Overall, the processing of the SAE data, the reporting and the tracking of the transmissions and submissions are associated with a high GCP risk. To mitigate this, a robust business process documented in an SOP and followed by trained staff (including the investigators) is essential.

Furthermore, constant monitoring of the compliance is necessary to ensure accurate and timely reporting.

5.9.1.3 Validation Approach and Challenges

Validation of all systems involved in the processing of AE data should focus on:

- Ensuring that the data is processed and no cases are lost. Cases that are lost in the processing due to incorrect workflows or staff availability have a direct impact on regulatory compliance.
- Correctness of SAE data on the report forms or in the electronic reports (ICH E2B(R3) [61, 62]). All required items must be correctly included. Special attention should be given to whom might be able to see unblinded information. It must be avoided that such unblinded information is available or transmitted (in blinded studies) to the investigators and/or the study team.
- Correctness of the aggregate reports required for development safety update report and similar other periodic reports.
- Tracking functions for SAE/SUSAR reporting to ensure that compliance can be monitored and compliance data is available for inspections and audits.
- Tracking requests for follow up information.
- System availability, backup and restore, as well as business continuity due to regulatory timelines.

Because of the diversity of the local requirements for SAE/SUSAR reporting (e.g., required report forms) validation of a drug safety system is often very detailed and time consuming. If a drug safety system is implemented or upgraded and a migration of data is necessary, a sample of the migrated case data should be verified to ensure correctness of the migration.

5.9.1.4 Typical Associated System Classes

Even though there are a number of COTS drug safety systems available, pharmaceutical companies and CROs commonly have custom developed systems, too.

Often the COTS systems for drug safety/pharmacovigilance require extensive configuration or customization especially if they are used on a global scale. These systems are typically classified as GAMP Category 4 or 5, depending on the level of customization.

Furthermore, drug safety systems often interface with other systems like coding tools (for MedDRA [46] and drug coding), and EDC systems (for SAE data transfer). To ensure that SAE processing is completed in a timely manner consistently, the interfaced systems must be setup for the same level of high availability as the drug safety system itself.

If the drug safety system consists of several applications that exchange data, the systems (including the interfaces) can be validated individually; however, the ability to fully support the business process must be verified and documented.

In summary, the majority of all validation activities are located in Layer II of the validation layer model unless study-specific interfaces are required (e.g., to EDC systems).

5.9.2 Sub-process: SAE Reconciliation

5.9.2.1 Short Process Description

It is common for safety data from a clinical study to be collected in several systems. For example, an EDC system may be used for capturing AE data on a site level, but SAE reports may also be collected using an email or fax addressed directly to the pharmacovigilance team, leading to the capture of that data into the separate pharmacovigilance database.

In order to ensure data integrity, it often becomes necessary periodically to reconcile SAE data between systems used for drug safety purposes and other systems such as EDC or CTMS. Any discrepancies must be investigated and resolved.

5.9.2.2 Data and Risks Associated with the Process

This process potentially has a direct impact on the safety of the subject. Failure to maintain data integrity across multiple systems might, at worst, result in the continuation of a trial with unacceptable risks to subject safety.

The safety data may be exchanged between systems electronically and automatically via interfaces; however, due to the project nature of clinical studies, the transfer of data for individual studies may also be manual.

If the exchange is electronic and automatic, a thorough validation and monitoring of the interfaces may reduce or eliminate the need for frequent data reconciliation. But any manual transfer of data between systems will require a sound reconciliation process. This process can be supported by database reports or more sophisticated applications.

Depending on the systems requiring reconciliation, the study, and the risk to the subject, the data elements to be reconciled must be determined and documented.

5.9.2.3 Validation Approach and Challenges

Validation for all systems involved in the reconciliation of the safety data should focus on:

- Accuracy of data in the reconciliation tools

- Automated filtering or highlighting of data (e.g., in reports that only display discrepancies between systems or use color coding)
- Notification services provided by the system to maintain regular reconciliation schedules
- Tracking of performed reconciliation reviews/activities

Due to the varying requirements from study to study, special attention must be paid to the combination of the reconciliation process, the supporting tools, and the qualification of the staff involved.

It should also be noted that parts of the other involved systems included in the processing of safety data (e.g., EDC, CTMS) may “inherit” part of the GCP-risk associated with the safety process.

For example, if a study uses an EDC system to capture the SAE data at a site, the relevant part of the EDC system must be validated as part of the safety system. System availability, backup and restore, as well as business continuity due to the regulatory timelines must also be considered. In this example, it could mean that acceptable downtimes for the EDC system may be as short as that for the safety system.

5.9.2.4 Typical Associated System Classes

Generally, reconciliation tools are either more or less sophisticated database reports that are checked manually, or tools that display the data side-by-side, and allow for inclusion/exclusion and commenting; however, all corrections must be made in the source systems after the discrepancies have been investigated.

All tools (database reports and special reconciliation tools) are either customized or configurable to enable them to connect various systems and extract the relevant data, and often are classified as GAMP Category 4 or 5.

5.9.3 Sub-process: Signal Detection and Proactive Pharmacovigilance

5.9.3.1 Short Process Description

In order to monitor and possibly refine the safety profile of the IMP (and then evaluate its risk-benefit profile), all safety data has to be evaluated continuously for unknown drug-related risks or new information on known risks (signals). This evaluation may begin with the review of an individual case report/SAE report, but generally includes the review or statistical analysis of aggregated safety data (ideally from all available sources).

A signal can be raised by an individual case of a highly unusual SAE, but more often signals are triggered by aberrations seen upon review of cumulative data or by statistical outliers in defined variables detected in the safety data.

Each potential signal must be tracked, investigated, and documented. If the analysis of the detected signals reveals that it negatively influences the risk-benefit balance for the trial, it may lead to a change in the study design or the termination of the study due to safety concerns.

5.9.3.2 Data and Risks Associated with the Process

This process potentially has a direct impact on the safety of the subject. The continuous monitoring and analysis of the safety data is a key element in the subject safety concept of a trial.

Depending on the study, the analysis may focus only on the data captured in the safety system itself or include other data (e.g., the FDA Adverse Event Reporting System (FAERS) [65]). Incorporating other datasets into the analysis has the advantage of allowing a comparison of the safety profile of the IMP with other products of the same class.

As an unfavorable risk-benefit balance might lead to the termination of the study to avoid further risks to the subjects, the GCP risk associated with this is high.

5.9.3.3 Validation Approach and Challenges

Validation for all systems involved in signal detection and proactive pharmacovigilance should focus on:

- Automated alert systems (e.g., when new cases meeting specified criteria are entered in the safety system)
- Accuracy of statistical calculations
- Automated filtering or highlighting of data (e.g., in reports that only display potential signals and may use color coding)
- Functions and tools that track the status, investigations, and actions for a (potential) signal
- Notification services provided by the system to maintain ongoing monitoring schedules
- Tracking mechanisms for reviews performed

Due to the varying requirements from study to study, special attention must be paid to the combination of the signal detection process, the supporting tools, and the qualification of the staff involved.

5.9.3.4 Typical Associated System Classes

The process and tools for signal detection vary greatly, often depending on the amount of data to be processed and evaluated.

For smaller trials, it is sufficient if all potentially relevant AEs are reviewed in the safety system as part of the day-to-day processing. For mid-size studies, the data may be reviewed and evaluated using standard tools like spreadsheet programs with or without macros. For large studies, specialized COTS tools are available; however, custom tools, e.g., based on SAS are common, too.

All tools (spreadsheet programs and special signal detection tools) are either customized or highly configurable to enable them to connect to multiple data sources, extract the relevant data, and detect signals, and should be classified as GAMP Category 4 or 5.

5.10 Process: Mid-Study Changes and Change Management

5.10.1 Short Process Description

Study protocol, amendments, and consecutive eCRF changes are likely to be the norm and not the exception. Changes can range from small eCRF corrections, like format of entry fields, to a complex re-design of the eCRF, for example if additional treatment arms need to be implemented.

A standardized and robust process for change/configuration management should be defined as part of the overall structure for the EDC/trial system life cycle.

A prerequisite of any mid-study change is the thorough definition of change specifications and a risk analysis. All specifications need to be approved before programming starts. The project manager will create a project plan that outlines the timelines and necessary resources for the change process.

All changes and updates of study materials must be communicated and delivered to the relevant partners, such as the sponsor or CRO/EDC vendor (whoever initiates and subsequently organizes the amendment), principal investigators and sites, pharmacies, as well as authorities and (local) ethics committees.

With protocol amendments, changes in all parts of the study are possible. Often small changes in study scope are followed by an update of many study documents, which logically might require the same effort as study initiation. Managing such changes is only possible with defined processes (SOPs) and open communication lines.

In addition, changes may not be applicable to all sites, depending on different regulatory requirements for example. Also, approval of different ethics committees may not be obtained at the same time.

Last but not least, investigation is needed to determine if the changes should be implemented prospectively or also retrospectively. In the latter case, it may be necessary that the site staff revisit the eCRF, because entry fields may have changed and signed pages may have become “open” again.

5.10.2 Validation Approach and Challenges as well as Typical Associated System Classes

Protocol amendments might affect all parts of the clinical study, with the potential to influence all systems used in a trial, indicating that the validation might be affected as well.

The first step of the validation approach is to identify the affected systems and define the changes following the change management approach used for each system, which means identifying the documents to be revised for this change and going through the whole software life cycle again.

Typically, the eCRF is part of the change and therefore the EDC system is mostly affected by such mid-study changes, but also other systems, e.g., pharmacovigilance tools or alert systems can be affected. Changes have the potential to require revalidation of a system. Ideally, this is performed by suitably qualified members of the (initial) validation team.

5.11 Process: Statistical Analysis and Programming

5.11.1 Short Process Description

Statistical analysis of the study data is performed according to the statistical analysis plan. This may include interim analyses, e.g., to adjust the sample size or to terminate the study prematurely. Statistical analysis typically includes the programming and/or configuration of a statistical system. It is recommended to follow the SDTM and Analysis Data Model (ADaM) data standards.

During the initiation phase, statisticians calculate the sample size of the study. The statistical evaluation phase includes the creation of tables, listings, and figures according to the statistical analysis plan using statistical software.

Also, statistical tests are performed and documented. The tables, figures, and listings form part of the statistical analysis report and will be key elements of the CSR.

5.11.2 Data and Risks Associated with the Process

Input data for statistical analysis and reporting can be all the clinical data in the study database. It has to be ensured that statistical programmers and statisticians use the correct input data for their work. This data must be released for further use by the clinical data management team.

Also, most statistical reporting involves the configuration or programming within statistical analysis systems. Results must be stored safe from later manipulations, and it needs to be transparent and traceable as to which input data and codes have been used to create which statistical results.

The main risk associated with this process is that incorrect statistical results become part of the CSR and are submitted to health authorities; therefore, the risk to data integrity is high.

The risk to subject safety is medium, as no immediate analysis of AE data is performed (that is covered in the process SAE reporting).

The general risk to subject safety is driven by the fact that errors in the statistical analysis can lead to incorrect data about the safety profile of a product. The overall GCP risk is, however, still high.

By repeating statistical computations with varying inclusion/exclusion lists, there is the risk that statistical testing can be manipulated so that the outcome is in the interest of the study sponsor.

The use of the ADaM creates an extra dataset between the SDTM data and the analysis computations. This makes the selection and processing (e.g., derivations and imputations) of data that is performed before the statistical analysis step considerably more transparent.

5.11.3 Validation Approach and Challenges

Validation includes the platform system used (e.g., SAS or R (statistical program)) and each custom-developed or configured program used for statistical analysis.

The validation of the platform system should focus on:

- Setup of statistical systems, which must be such that it is later possible to reconstruct which result files were created by whom based on which input data and which program files.
- Ensuring that the input data is correct and cannot be manipulated. The interface to the clinical study database needs to be validated, or the import process needs to have adequate quality control steps. The prerequisite for statistical analysis is that the clinical data has been released for further use by the clinical data management team.
- Output files need to be protected from later manipulation.
- Repetitions of statistical computations need to be visible and justified, especially if inclusion/exclusion lists are changed.
- The interface and data transfers to the systems used to create the CSR needs to be validated.

The validation of study-specific programs should focus on the correctness of the statistical computations. Typically, the statistical analysis plan can serve as the specification document for statistical programming; therefore, often no additional specification documents are needed.

For study-specific programs, validation approaches such as peer review or double programming are suitable. Peer review is often acceptable if study-specific programs are configured and call fully validated standard programs. If study-specific programs involve more custom programming, then double programming or functional testing should be used. Also, double programming or functional testing should be used for the generation of key analysis results.

It is a specific challenge of statistical analysis systems that they contain not only clinical data and standard functionalities, but are also used as programming environments for statistical analysis codes; thus, user management and the definition of rights and roles need special attention. Often, there are development, test, and production servers (for platform-wide updates and changes), and each contains development, test, and production folders for study-specific programming and testing.

Most statistical platform systems are very powerful programming environments and have a tendency to attract business processes from many different departments, ranging from the analysis of logistical dose-response relationships, signal detection for pharmacovigilance, in-process control for manufacturing, to econometrical computations.

It needs to be transparent which business processes are supported by a statistical platform system, and which standard programs support what kind of business process. The business processes supported by the platform need to be documented and considered during design of the platform, otherwise the system may not be fit for purpose.

For example, if the statistical platform is also used to store unblinding data, e.g., randomization lists, the user account management needs to be considered during system planning so as to avoid unblinding to all personnel with read access to the system.

5.11.4 Typical Associated System Classes

Typically, a platform system (Layer II) is the basis for statistical reporting. While these platform systems are COTS in principle, considerable configuration is normally required to enable platform functionalities such as folder structures useful for programming and clinical studies, roles and responsibilities, and audit trails/log files. Therefore, the platform systems very often are GAMP Category 4 or 5.

The study-specific analyses programs (Layer III) are usually configured or custom coded and therefore also are GAMP Category 4 or 5.

Either the platform or the study-specific programs should be GAMP Category 5, because for some statistical analyses, some custom programming is nearly always needed.

5.12 Process: Study Report, Study Closure, and Submission

Based on the clinical data and the statistical analysis results, the study report is created and submitted to health authorities and responsible ethics committees.

All study results are archived in the TMF. All source data is archived at the site of data generation, e.g., the investigator site. This data needs to be archived for the time frames specified in the regulatory requirements.

Also, the study results are published and the study data is made available to the scientific public.

5.12.1 Sub-process: Clinical Study Report Generation and Creation of the Submission Package

5.12.1.1 Short Process Description

The Clinical Study Report (CSR) is a written description of a study conducted in human subjects, in which all relevant documents and information are integrated into a single document.

This is in part based on the statistical analysis report, which is the output of the statistical analysis process. This type of report also includes tables, figures, listings, and appendices containing the protocol, and details such as sample CRFs, investigator related information, investigational medical product information, technical and statistical documentation, related publications, and listings of subject data, such as AEs.

Also, the clinical data is part of the CSR, for example in a CDISC compliant format, e.g., SDTM. Several document format and data standards apply, e.g., electronic Common Technical Document (eCTD) and Identification of Medicinal Products (IDMP). In particular, the IDMP standard can require interfaces to systems from the manufacturing area, or specific efforts to have the necessary data available.

Interim study reports can be published during the runtime of the study but need to be planned in advance in the clinical study protocol.

5.12.1.2 Data and Risks Associated with the Process

Overall, the data related to the study is used in the creation of the CSR.

The main risk is that data is incorrectly represented in the report, or that specific documents or sources of information are not considered when creating the CSR. The business impact of such an error would be high, because incorrect or incomplete data would be submitted to health authorities in that case. This would lead to delays in the marketing authorization process, because errors in source data or statistical results will be found with a high probability.

The same applies to the submission package. Therefore, the risk is considered to be medium.

5.12.1.3 Validation Approach and Challenges

In general, text editing systems do not need to be validated because the user sees immediately the output and can verify it, as long as no calculations or macros are used (typewriter exclusion).

Often integrated document management systems are used when creating the CSR, which also ensure conformance to the applicable data and formatting standards.

Templates used for the CSR creation should be controlled. Also, any custom-made macros used should be validated.

A structured review of the created CSRs based on a clear procedure with defined criteria is paramount to ensuring their quality. Separate tools/systems can be used to support the review process. Furthermore, there are DMSs with integrated functionality for collaborative editing and review.

If eCTD documents are created from the start of the study, the system used should be validated to ensure the correctness of the resulting XML files.

Additionally, creating and maintaining the necessary data for the IDMP standard can require interfaces with systems from the manufacturing area.

5.12.1.4 Typical Associated System Classes

Typically, standard office systems are used to create and compile the CSR, which is GAMP Category 3; however, the typewriter exclusion applies to standard document editing systems, so they do not need to be validated.

The document management and publishing system used to bundle the different documents into the complete submission, including formatting according to the applicable standards, usually needs validation. Often, GAMP Category 4 applies to DMSs.

5.12.2 Sub-process: Medical Writing and Data Transparency

5.12.2.1 Short Process Description

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Medical writing is the creation of scientific documentation by specialized writers with a medical background. They work together with the investigators and clinical staff (who produce the scientific study data) to create documentation effectively describing the meaning of the clinical data collected during the study, complying with regulatory, journal, or other guidelines in terms of content, format, and structure.

Documentation provided by medical writers includes protocols, subject information, leaflets, CSRs, safety updates, clinical expert reports, training materials, as well as input for marketing documents, advertisements, posters, literature reviews, abstracts, and manuscripts for publication.

There are regulatory requirements concerning the publication of clinical study results and the provision of the clinical study data to the scientific public. For a discussion of data, risks, and systems involved see Section 5.12, because the processes, data, and systems used are often very similar.

5.12.2.2 Data and Risks Associated with the Process

Protocol amendments might result in changes of the whole process of conducting a clinical study and, therefore, all systems used in that trial. Change management is typically a high-risk process, as a small change in one part of the study might have unpredictable consequences for the systems used in the trial.

Risk-based validation is mandatory. Each process has to be analyzed (is it affected by the change or not?) and the decision about validation activities needs to be risk-based and documented.

5.12.3 Sub-process: Creation of the TMF and ISF

5.12.3.1 Short Process Description

Note: according to ICH E6(R2) [5] terminology, both the Trial Master File (TMF) at the sponsor and the Investigator Site Files (ISF) are called TMF. In this Chapter, the terms TMF and ISF are used for a clearer distinction.

The TMF is a central filing system maintained by the sponsor containing all documents related to a clinical study, including contracts with the trial sites and third parties, regulatory approvals, insurance, indemnification, GxP certificates, and essential documents associated with the investigator sites participating in the study. Basically, all documents that individually and collectively permit the evaluation and reconstruction of the conduct of a trial and the quality of the data produced is contained in the TMF

In addition, the TMF includes transcripts of the investigator site files (except individual study participant data).

The purpose of each TMF document/file should be clearly described. It can be maintained either on paper or in electronic format (eTMF); however, storage of the TMF should not be difficult to access.

TMF maintenance and archiving ranges from study planning over study conduct to post completion (in compliance with the national and international retention periods).

The TMF format should be secure and should allow easy retrieval of data and information for audits and regulatory inspections to enable the evaluation of the conduct of a clinical study and the quality of the data produced. Evaluation as to whether or not investigators and sponsors have complied with the principles and guidelines of GCP and with the applicable requirements is included.

5.12.3.2 Data and Risks Associated with the Process

The main risk is incorrectly or incompletely stored data in the TMF, or that specific documents or sources of information are not considered when creating the TMF.

If paper documents are scanned and converted to PDFs for storage in the eTMF or the ISF, scanning errors can occur (missing pages, unreadable pages, notes on the back of pages missing, lightly written manual notes not visible, automated pattern recognition changing letters or digits).

Destruction of paper originals should only be performed in conjunction with a rigid and documented scanning process quality assurance and quality control program, because if scanning errors are detected later, the damage is irreversible and often results in a loss of data.

Some of the content of the eTMF will be included in the submission and specific data formats apply, see Section 5.12.3 and Section 5.12.4 for details.

In practice, often the focus is on the conduct of the study and submission of the results, and the TMF and ISF creation process is inadequately managed and performed. Overall, the risk is high.

5.12.3.3 Validation Approach and Challenges

The process of creating certified digital copies of paper source documents needs to be validated, as well as the systems used. Or there needs to be documented quality control of all PDFs, comparing them to the paper original.

While certified digital copies are often accepted at inspections, it is strongly recommended to retain and archive the paper source documents, due to the risk of scanning errors being detected after the destruction of the originals. Also, the legal situation in some major European countries is unclear. Especially in the case of Informed Consent documents, the destruction of paper originals is discouraged.

When moving electronic records or documents to the eTMF, it needs to be evaluated which metadata also need to be moved, e.g., electronic signature or audit trail information. The DMS used as an eTMF or ISF needs to be validated as well. Usually, no trial-specific configuration is performed beyond the definition of metadata and setup of specific folders.

There is a growing expectation among inspectors to be provided with a read-only access to the eTMF. This access needs to be limited to the study that is being inspected.

eTMFs are sometimes transferred from CROs to the sponsor. This transfer and other aspects of the eTMF life cycle need to be planned and must occur in a controlled, verified, and documented way.

The eTMF needs to contain all documents and records essential to reconstruct the conduct of a clinical study.

This definition is very general and therefore covers a lot of documents sometimes not associated with an eTMF, e.g., training records or validation documentation of the computerized systems used. It is usually accepted that these records are managed in separate systems (e.g., a training system or a DMS); however, clear references to these systems need to be in the eTMF.

5.12.3.4 Typical Associated System Classes

eTMF systems range from GAMP Category 3 to GAMP Category 5. Sometimes, these systems are add ons or sub-systems of existing DMSs. They are often GAMP Category 4. Also, the eTMFs are usually part of the Study Reference Architecture (SRA).

5.12.4 Sub-process: Submission of Study Closure to Authorities and Ethic Committees

5.12.4.1 Short Process Description

According to national and international laws, the end of a clinical study must be declared to competent authorities and, if applicable, to ethics committees. Usually, the end of a clinical study should be described in the clinical study protocol.

In addition, a final study report needs to be submitted.

Timelines for both, notification and final study report submission, differ depending on:

- Country of study conduct
- Reason for end of clinical study (regular, premature)
- Kind of study product (medicinal product, medical device)

- Type of study population (adults, children)

Since clinical studies involving human subjects need to be registered in a publicly accessible database, the notification of end of trial is usually carried out through these databases. Associated documents might have to be sent to local authorities or ethics committees.

If the results of a clinical study lead to a marketing application, the corresponding final study report needs to meet the standards of the ICH E3 guideline [66].

5.12.4.2 Data and Risks Associated with the Process

The task of notification does not contain any subject or study data other than the dates of the beginning and end of the clinical study. Even the risk of forgetting the notification is usually under control with the use of SOPs and trial specific checklists.

This is different for the data in the CSR. Although the data stated in the report is a validated output of the EDC and statistical systems, there is still a risk of documenting data in wrong sections of the report.

5.12.4.3 Validation Approach and Challenges

No validation approach is necessary with regard to the notification. If the sponsor or sponsor's representative forgets the notification, results will not be published, marketing approvals will not be filed and a fine can be handed out by health authorities. This is a business impact.

For the study report, usually written in a text program, the data and outcomes described need to be checked against the output and tables extracted from the database. Data validation processes will be done earlier during the stage of data processing within the EDC system.

5.12.4.4 Typical Associated System Classes

Word processing programs normally do not have to be validated, according to ISPE GAMP® 5 [3]; nevertheless, the data summarized in the end of study report needs to be verified against the initial output of the database to ensure accuracy.

5.12.5 Sub-process: Data Transfer to Authorities and Partners

5.12.5.1 Short Process Description

Data transfer to authorities and partners requires a defined data set and structure (e.g., eCTD) performed at defined time points throughout the study. The eCTD contains considerably more data and documents than those created during the course of the clinical study, e.g., documents related to the production and analysis of IMP.

Also, questions from the health authorities and the proof-of-acceptance documents need to be received, managed, answered, and stored.

5.12.5.2 Data and Risks Associated with the Process

During transformation to a different format, there is a risk that data is corrupted or missing in the target format.

Additionally, during transfer to health authorities, information can be corrupted or lost. References within the eCTD format might need to be corrected. Checksums are used to verify the integrity and completeness of the data transfer.

The overall compliance risk is considered low, because if incorrectly formatted data would be submitted to health authorities they would be detected automatically during the data upload. However, there is a considerable business risk because of potential delays. Validator tools can be used by the sponsor to check for format correctness before the upload.

Also, questions coming back from the health authorities and the proof-of-acceptance documents need to be received, managed, answered, and stored.

5.12.5.3 Validation Approach and Challenges

EMA and FDA own and provide web portals for the upload of submissions. While these do not need validation by users, the process used to upload documents should be validated on the sponsor side, e.g., to ensure that the right documents are uploaded.

Moreover, the systems used to manage questions from the health authorities and proof-of-acceptance documents need to be managed, as well as format-validator tools.

5.12.5.4 Typical Associated System Classes

As the health authority owns the web portals for data transfer, only the document management and publishing systems that create the submission package and that manage questions back need validation. These are often GAMP Category 4 or 5, similar to the systems used to create the submission package.

5.12.6 Sub-process: Archiving

5.12.6.1 Short Process Description

All study documents need to be collected in the TMF and/or ISF. After study closure, these files need to be archived by both parties following country-specific regulations. Refer to the *ISPE GAMP® Good Practice Guide: Electronic Data Archiving* [67].

Collecting all study relevant paper documents and storing them either in the TMF or ISF is essentially administrative work, but the process is clear (see Section 5.12.3).

Since it is state of the art that clinical study data is collected in electronic systems, the process of storing a copy of the collected data has to be adapted to the electronic approach. A risk-based approach should be taken. For each system, it should be determined:

1. Whether the data needs to be kept in a way such that it is fully reprocessable
2. Whether it is sufficient to be able to view and search the data
3. Whether it could be sufficient to view only individual data sets

It should also be decided which data and metadata need to be archived.

For example, for a study-specific EDC system that contains key study data and in which many data changes were performed as part of the data clarification process, it is usually appropriate to archive the EDC as a fully functional relational database. This guarantees that it can later be understood how the data was entered and processed, and which roles had which views and access rights. Technically this is possible by using virtual machines. The same applies to other high-risk data such as electronic patient diary data or AE data.

On the other hand, for the training documentation of the study team held by the sponsor, it may be sufficient to archive a flat file of the training system database, including both the data and the metadata.

Additionally, the risk of the study should be considered: data from a study that will be part of a submission to health authorities usually needs a higher standard of archiving than an investigator initiated trial performed to create a scientific publication.

Even if a lot of study work is outsourced, e.g., to CROs, ultimately the records need to be available quickly and completely, e.g., during sponsor inspection. Agreements need to be in place with all involved parties to guarantee this.

As an example of archiving considerations, the archiving of an EDC system is discussed in more detail.

In studies where the clinical data is collected on a paper CRF, the CRFs are printed on carbon paper. The site sends the original to the sponsor's delegate for data management (e.g., CRO) and stores the copy in the ISF. The site owns the copy; it will never leave the site.

In studies where an electronic system is used for data entry, the site does not own a copy, but has access to the eCRF for the complete study life cycle.

After study closure, the sponsor is responsible for providing a copy of the eCRF screens to the sites for archival; however, electronic source data regulations apply [27].

Once the final datasets are approved and the database closed, the eCRF archival process begins. The eCRF-screens for each patient and site must be printed in a long term readable format (PDF). The archival files must be crosschecked with the original eCRF screens for legibility, invalid characters, and truncations.

To imitate the complete paper CRF, the audit trail per page, the signature status, and history of the page and the queries (including their history) should also be part of the screens, or could be added as tables or another suitable format. The files should be encrypted and saved on an electronic medium (e.g., DVD).

The readability of the electronic medium must be guaranteed throughout the retention time of the source data.

Also, the regulations for electronic source data apply, e.g., that the sponsor must not have sole control over electronic source data, or during the creation of permanent data storage medium (CD/DVD/BlueRay), although this may legitimately not apply to studies where the same entity/legal person assumes the sponsor and investigator roles.

Each site receives an electronic medium with the data of their patients; the sponsor gets a complete set of these eCRF screen copies. The site needs to acknowledge the receipt of the data, to approve that they could encode and open the files, and know how long and how to store them.

After all acknowledgements are collected, the system itself is ready for archival.

The archiving of the EDC system should include:

- The electronic system with its underlying infrastructure on a virtual machine
- The validation documentation

However, risk-based consideration may apply (see above).

Both in the TMF and the ISF, relevant metadata needs to be included, and data and metadata should be searchable or viewable to answer questions such as: which were the changes and deletions related to a specific subject, and which were the overall changes and deletions?

In the case of an ISF, data and metadata also need to be limited to data relevant to the site.

ALCOA principles apply throughout the data life cycle including archiving.

5.12.6.2 Data and Risks Associated with the Process

The archival files could be incomplete and therefore bear the risk that it is not possible to reconstruct the complete history of each data field according to the ALCOA+ principle. The archiving process usually has the same risk as the process it supports.

5.12.6.3 Validation Approach and Challenges

The computerized archiving system should be subject to validation (see also *ISPE GAMP® Good Practice Guide: Electronic Data Archiving* [67]). The archiving equipment should be qualified.

5.13 Process: Quality Assurance and Quality Control

For the conduct of a study, it is mandatory to have a risk-based quality management system in place. The sponsor should implement an organizational system to manage quality throughout all stages of the trial process, ensuring that clinical studies are conducted and data is generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements (see ICH (E6(R1)), Section 5.1.1 [13]).

In implementing such systems, sponsors and service providers should focus on trial activities essential to ensuring human subject protection and the reliability of trial results (i.e., derived from trial data).

The scope of quality management activities must encompass the entire clinical trial life cycle, including the design of efficient clinical trial protocols, processes, and tools for collecting and processing data and information (including computerized systems), especially those essential to decision making.

A risk-based approach implies that the methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial, the importance of the data collected, and the information derived from it.

The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, CRFs, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-management approach that contains the following phases:

- Critical Process and Data Identification
- Risk Identification
- Risk Evaluation
- Risk Control
- Risk Communication
- Risk Review
- Risk Reporting

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(See ICH E6(R2), Section 5.0 [5])

These principles should also be reflected in any risk-based approach to the validation of computerized systems (see *ISPE GAMP® 5* [3]).

Typical activities within quality management are quality assurance and quality control activities. These include planned operational techniques such as clinical monitoring as well as systematic approaches like audits for all aspects involved in the conduct of a clinical study.

All determined nonconformities to the protocol, SOPs, and applicable regulatory requirements need to be documented, assessed, and tracked. Appropriate steps should be taken to prevent any recurrence. This is known as the Corrective and Preventive Action (CAPA) process.

Monitoring is ideally performed at the site to ensure patient safety, accuracy, and completeness of the data reported as well as to confirm study conduct in compliance with the protocol and applicable regulatory requirements. To do so, the clinical monitor compares the source documentation with the respective entries of the CRF. Besides potential health record systems or the EDC system, no additional components are required (for details see Chapter 5.8.3 Sub-process: Monitoring).

5.13.1 Sub-process: Audits

5.13.1.1 Short Process Description

Auditing is independent supervision of all study related activities and documents to confirm that each step of trial conduct is performed in compliance with the protocol, sponsor SOPs, quality agreements, and applicable regulatory requirements including data documentation, analyzing, and reporting. This includes all involved parties in a clinical study such as clinical sites, laboratories, EDC providers, and CROs.

Ideally, the sponsor also conducts voluntary audits performed by an external party for all tasks performed by the sponsor to ensure that all sponsor responsibilities are covered.

Audits can be performed prior to the conduct of a study and/or during the course of a study. Typically, potential suppliers should be qualified through an audit process prior to their participation to determine if the organization will be able to perform tasks according to protocol, SOPs, and applicable regulations.

Audits performed during the conduct of a study should ensure that all parties such as sites, suppliers, and sponsor personnel follow the contracted and regulatory requirements (see also Section 5.5 Process: Site/Partner Qualification).

5.13.1.2 Data and Risks Associated with the Process

It is recommended to establish a risk-based approach when identifying audits to be performed (including for-cause audits); thereby, all involved parties and tasks with a critical aspect to subject safety and data integrity can be identified and audited as early as possible to avoid unplanned postponements. This applies to suppliers of critical items prior to the beginning of a study as well as to involved parties during the conduct of a study.

To be able to maintain oversight it is advisable to establish a tracking system that allows audit planning, information on audit performance and outcomes (refer to Section 5.13.3) along with possible re-audit time frames depending on the outcome of the audit.

Furthermore, audit reports need to be created, reviewed, approved, communicated internally and externally, and audit responses considered/implemented.

A main risk is that organizations or sites critical to a study are not audited. In addition, there is a risk that audit outcomes are not followed up correctly resulting in observations that are not addressed.

Overall, these risks have an indirect impact on the quality of the study, and therefore the risk is considered medium.

5.13.1.3 Validation Approach and Challenges

The systems used for audit planning, reporting, and CAPA tracking must be validated. Typically, these systems have a limited number of users who are part of the QA organization of the sponsor; thus, training and SOPs can be managed internally. Additionally, the infrastructure used to access these systems is generally under the control of the sponsor.

5.13.1.4 Typical Associated System Classes

Often, a customized system can be used for audit planning, reporting, and CAPA tracking; thus, it is GAMP Category 4.

Auditing is like a standard process, and the project nature of clinical studies does not impact the involved systems as much as for other systems. Systems supporting this process are mostly at Layer II.

5.13.2 Sub-process: SOPs and Training

5.13.2.1 Short Process Description

All aspects of a clinical study covering the conduct, or contributing to patient safety or data integrity, need to be supported by written and up-to-date SOPs. This means that not only does the sponsor need to have SOPs in place but also all other involved parties such as suppliers.

An up-to-date SOP system tracks or controls the approval processes, review cycles as well as training of all involved staff members. In addition, adherence to a given procedure needs to be verified.

Furthermore, the qualification of each team member involved in a clinical study has to be maintained and documented. This includes sponsor staff such as data managers and biometrists as well as all supplier staff members.

5.13.2.2 Data and Risks Associated with the Process

Document control of SOPs can be performed with a DMS that supports approval processes with the use of electronic signatures. Once an SOP is approved and released for use, all team members should be able to access the valid document at any time.

The main risks are limited access to SOPs, and the use of outdated or incorrect SOPs during study work. This impacts data integrity and subject safety indirectly; therefore, the overall risk is medium.

The documentation of qualification and training of team members can be done electronically in a tracking system. The main risk here is the possibility of untrained staff performing GCP-relevant activities. Depending on duty (e.g., data collection versus data analysis) and location of the staff (e.g., sponsor vs. site) the related risk can vary from medium to high.

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5.13.2.3 Validation Approach and Challenges

The systems used for document management or tracking of qualification and training must be validated. Typically, all involved parties have their own systems for their SOPs and training management. This creates challenges for the collection of all training documents into the TMF.

5.13.2.4 Typical Associated System Classes

Often, a configured system can be used for document management, review, approval, training; thus, it is GAMP Category 4. This is essentially a standard process, and the project nature of clinical studies does not impact the involved systems. Systems supporting this process are mostly at Layer II.

5.13.3 Sub-process: CAPA, Serious Breaches

5.13.3.1 Short Process Description

Issues can be detected by several means, such as through audits, self-reporting, or notification by the provider hosting a system. Once classified as GxP-relevant, an investigation needs to be performed to identify the root cause and to assess the impact. Based on this, CAPA are defined, tracked to completion, and verified by effectiveness checks. Incoming issues are analyzed for recurring trends to adjust the preventive actions.

A similar process applies to protocol breaches, including serious breaches and on-time communication with the health authorities.

5.13.3.2 Data and Risk Associated with the Process

Data involved can be information on computerized systems, processes, data, and people connected to the study. If only issues and CAPAs are managed in the system, then the risk for study subjects and data integrity is indirect, and therefore medium. If serious breaches are managed in the system, then the associated risk is high.

A large data integrity risk involves issues and breaches that are not reported and documented in the CAPA system but managed outside of it, not following the established process; therefore, the entry of an issue into such a system should be allowed by as many users as possible.

5.13.3.3 Validation Approach and Challenges

The validation of CAPA systems is often approached like that of any internal system at a sponsor or a CRO; however, the ownership of investigations or CAPA items can be at any of the organizations involved in a study, e.g., clinical sites. This often leads to hybrid processes with paper forms, because only internal personnel have an account in the CAPA system. These processes are often inefficient and carry data integrity risks.

5.13.3.4 Typical Associated System Classes

Systems used for issue and CAPA management are usually COTS or may contain custom coding and so are classified as GAMP Category 4 or 5. This is essentially a standard process, and the project nature of clinical studies does not impact the involved systems. Systems supporting this process are mostly at Layer II.

5.14 Process: Laboratory Analysis and Sample Logistics

If the study includes any laboratory testing, the logistics for the samples need to be in place, including environmental controls as required. The data transfer from the laboratories to the data management organization must be defined, established, and controlled.

5.14.1 Sub-process: Logistics and Analysis of Samples

5.14.1.4 Short Process Description

Within a clinical study, many samples taken from the subjects need to be analyzed to prove the effectiveness of the drug as well as to monitor subject safety. Tracking and proper handling of the samples is essential to ensure correct and complete data.

Often the analysis is not done on site, so tight control of the logistic process involved is essential. This includes control of time, environmental conditions, and routes.

Furthermore, training of the staff at the site is needed to ensure adequate sample labelling and handling. Blinding needs to be maintained at all stages.

Samples are analyzed for parameters defined in the study protocol.

5.14.1.2 Data and Risks Associated with the Process

Essential data are subject numbers, sample identifiers, shipment data, environmental condition data, analysis method parameters, and analysis results.

Potential risks are the incorrect labeling, storage, and transport of samples, leading to loss, mix up, or expiration of samples. Also, inadvertent unblinding is possible.

Concerning analysis, there is a risk that the method is not adequate, or that it is incorrectly performed, both leading to incorrect data.

Additionally, the transfer of all relevant data back to the sponsor needs to maintain data integrity. Overall, the risk is high.

5.14.1.3 Validation Approach and Challenges

In sample logistics, one challenge is the multitude and potentially fast turnover of third parties involved, which often does not allow for the development and validation of automated interfaces between the different systems. Procedural solutions need to be found for processes like sample labelling or the collection of temperature logger data.

Sample analysis must use validated methods; computerized systems need to be validated in line with *ISPE GAMP® 5* [3].

Systems used for clinical analysis may also be used for other purposes; nonetheless, the systems need to be validated. Risk-based approaches can be used to scale the validation effort, e.g., for reports.

For analyses for clinical studies, the source data needs to be defined. Also, study-specific customizations may be needed.

Partners in logistics and sample analysis need to be qualified, and responsibilities clearly defined.

Validated systems need to be used, and interfaces validated. For example, for temperature loggers used to document sample shipment conditions, who evaluates the temperature data based on which acceptance criteria, and how excursions are evaluated and escalated needs to be clearly defined.

Also, the integrity of the temperature data needs to be maintained when communicating it from the laboratory to the sponsor.

5.14.1.4 Typical Associated System Classes

Sample and logistics management systems are generally GAMP Category 4 to 5. Environmental monitoring systems are typically GAMP Category 3.

LIMS, including reporting tools, are mostly GAMP Category 4 or 5. Systems used for laboratory analysis are for the most part GAMP Category 3 or 4.

5.14.2 Sub-process: Data Transfer from Laboratories

5.14.2.1 Short Process Description

From the analysis laboratories, data needs to be transferred into the clinical database.

For in-house laboratories and often-used central laboratories, an automated interface between the LIMS and the clinical database can be established and validated.

For external and infrequently-used laboratories, typically no automated interfaces can be set up. Instead, data transfer occurs by different means either on paper, or electronically, e.g., by mailing a CD, or via the internet, using File Transfer Protocol (FTP), email, or a web portal.

Data integrity and blinding need to be maintained during transfer.

5.14.2.2 Data and Risks Associated with the Process

Risks are that laboratory data related to subjects is corrupted, or the association to a subject number is mixed up. Also, depending on the study design, there may be unblinding issues. Overall, the risk involved is high.

5.14.2.3 Validation Approach and Challenges

Automated interfaces need to be validated.

Laboratories involved need to be qualified, and procedures for data transfer need to be defined, trained, followed, and validated, both at the laboratory and the receiving party.

If a manual data transfer is required, it should be performed on a medium on which the data cannot be modified during transfer (e.g., signed-off DVDs).

For transfers via the internet, secure methods should be used, such as sFTP. If email is used for speed, it should use file formats that are tamper-proof, e.g., by using encryption or hashtags; otherwise, email transfer should be backed up by a safe second way of transferring data.

5.14.2.4 Typical Associated System Classes

Automated interfaces are often custom programmed and are therefore GAMP Category 5. Manual data transfer processes do not fall into a system class.

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6 Data Integrity

As mentioned in Chapter 2, the integrity of the data collected and processed during a clinical study is an essential quality aspect. The following definition of data integrity should be applied.

6.1 Definition

Data integrity can be simply defined as the validity of data and its relationships. For electronic records collected and processed as part of a clinical study to be trustworthy and reliable, the links between raw data, metadata, and results must not be compromised or broken.

Without data integrity, it is not possible to regenerate a result of a clinical study reliably. Obviously, maintaining data integrity is a critical aspect not only for clinical studies and eClinical Platforms. It needs to be addressed throughout the product life cycle spreading across GMP, GLP, GCP, and other GxP areas.

The following definitions from the *ISPE GAMP® Guide: Records and Data Integrity* [68] further reinforce this importance:

- Regulated data is information used for a regulated purpose or to support a regulated process.
- Metadata is data that describes the attributes of other data, and provides context and meaning. Typically, these are data that describe the structure, data elements, inter relationships, and other characteristics of data.
- A regulated record is a collection of regulated data (and any metadata necessary to provide meaning and context) with a specific GxP purpose, content, and meaning, and required by GxP regulations. Records include instructions as well as data and reports.
- Data integrity is defined as the extent to which all data is complete, consistent and accurate throughout the data life cycle.
- The integrity of records depends on the integrity of underlying data, and signatures executed to electronic records should be trustworthy and reliable.

The ALCOA+ acronym is often mentioned in the context of data integrity as principles to be considered [68].

Table 6.1: ALCOA

Principle	Data Expectation
Attributable	<ul style="list-style-type: none">• Attributable to the person or system generating the data• Identify the person or system performing an activity that creates or modifies data• Linked to the source of the data
Legible	<ul style="list-style-type: none">• Readable and permanent• Accessible throughout the data life cycle• Original data and any subsequent modifications are not obscured
Contemporaneous	<ul style="list-style-type: none">• Recorded or observed at the time the activity is performed
Original	<ul style="list-style-type: none">• Original data is the first recording of data, or a “true copy” which preserves content or meaning
Accurate	<ul style="list-style-type: none">• Free from error• No editing performed without documented amendments• Conforming to truth or standard

Table 6.2: ALCOA+

Principle	Data Expectation
Complete	<ul style="list-style-type: none"> All data, and relevant metadata, including any repeat or re-analysis performed
Consistent	<ul style="list-style-type: none"> Application of good documentation practices throughout any process The application of date and time stamps in the expected sequence
Enduring	<ul style="list-style-type: none"> Recorded in a permanent, maintainable form for the retention period
Available	<ul style="list-style-type: none"> Available and accessible for review, audit, or inspection throughout the retention period

This Guide will not investigate every aspect of data integrity, but will focus on the specific aspects that should be considered in clinical studies.

Basically, in clinical research every activity (or lack of expected activity) must be documented. Or, to use some common phrases:

- “What is not documented is not done!”
- “Document what is done as well as what is not done!”

This is the essence of the good documentation principles in ICH E6(R2) [5] where source data and source documents are first defined.

6.2 Risks

On a high level, the risks for data integrity range from non-intentional to intentional incidents. These incidents can be classified as:

- Slips and lapses that are just part of being human
- Mistakes that are often made because there are insufficient controls or too much complexity
- Situational violations that occur when something unexpected happens and we just do the wrong thing
- Routine violations that involve doing the wrong thing over and over because it is easier and we think that taking that shortcut does not matter
- Optimized violations that are concerned ways of working to avoid a control and/or evade associated additional workload
- Intentionally misleading activities that are actions to cover unauthorized manipulation of data and fraud

These scenarios need to be addressed by controls that are defined and implemented.

While this Guide primarily focuses on technical and procedural controls, the behavioral, cultural, and management aspects are of importance too. More guidance on these aspects can be found in the *ISPE GAMP® Guide: Records and Data Integrity* [68].

6.3 Data Ownership and Governance

Data integrity is one aspect of data quality (alongside aspects such as fitness for use, etc.). Data quality, in turn, is one feature managed by an overarching data governance framework. Other features may be data privacy and data confidentiality.

Those aspects will influence the validation approach for the relevant systems and platforms, as the necessary controls need to be implemented and verified.

Within the data governance framework, it is customary to define roles such as:

- Data owners: those who “own” the data and have ultimate accountability for the data
- Data custodians: those who bear responsibility for the data as it passes “through their hands”

Any changes to data must be endorsed by the data owner. For instance, any data entered at site must not be changed without approval from the investigator. It should be understood that derived data (such as the statistical analysis of the site data) is often owned by the sponsor.

For example, in clinical studies, the investigator owns the source data, regardless of where the data is. The data may then be under the control of the sponsor, a central clinical laboratory, an EDC provider, or a central image reader, but the ownership is not transferred.

The sponsor on the other hand, owns the data derived in a data management process.

6.4 Data Life Cycle

In order to enable data ownership and governance, the data life cycle needs to be defined and enforced for all processes and data involved. The data life cycle starts from initial generation and recording through processing (including transformation or migration, review, and approval), use (including reports), retention, archive, retrieval, and destruction.

The life cycle serves to understand the complete handling of the data, following it over organizational and system boundaries. It is the basis for a comprehensive risk assessment that does not look at individual software packages or databases but at the processes involved.

For example, the transfer of eDiary data from a hosting vendor to the clinical sites and the sponsor is best analyzed when looking at the data life cycle.

By analyzing all processes involved, not only can technical risk mitigation measures be identified, but also contractual and procedural methods. An example of the latter is verifying that contractual agreements between the sponsor and the vendor ensure that all metadata will be transferred and that the features of the relational database are maintained.

While traditional approaches to computerized systems validation often start with a user requirements specification in which a few points from 21 CFR Part 11 [8] are copied, an approach focused on data integrity starts with the business process and the data life cycle.

In the following sections, GCP-specific scenarios and challenges are examined with regards to data integrity and its risks in the context of computerized systems, eClinical Platforms, and clinical trial documents.

6.5 Data Integrity in Computerized Systems Used in Clinical Trials: electronic Source Data (eSource Data)

Historically, GCP-relevant systems were very much limited to the pharmaceutical industry and their partners like CROs.

More recently, IT systems in hospitals and at investigator sites have been included in clinical studies processes and consequently are becoming increasingly GCP-relevant, for example, via the use of EDC systems at the site or the delivering sub-systems such as Electronic Health Record (EHR) systems.

As mentioned in Section 2.1.3, Control over Technology, Process, and Training, there are numerous risks originating from the high degree of outsourcing and the number of parties involved that can negatively influence data integrity. Furthermore, the source for any given data element captured as part of the clinical study, needs to be clearly understood. Inspectors routinely verify the quality and integrity of source data; therefore, a clear understanding of the origin of the data is essential.

According to the FDA Guidance for Industry: *Electronic Source Data in Clinical Investigations* [27]:

“Capturing source data electronically and transmitting it to the eCRF should:

- *Eliminate unnecessary duplication of data*
- *Reduce the possibility for transcription errors*
- *Encourage entering source data during a subject’s visit, where appropriate*
- *Eliminate transcription of source data prior to entry into an eCRF*
- *Facilitate remote monitoring of data*
- *Promote real-time access for data review*
- *Facilitate the collection of accurate and complete data”*

However, these benefits can only be achieved if the tools and process for data collection and capture are well defined and controlled.

It should be noted that the current guidance on eSource data in clinical studies from the EMA Reflection Paper [28] and the FDA Guidance for Industry [27] is not fully aligned in a number of areas, such as:

- In contrast to the FDA Guidance for Industry [27], the EMA Reflection Paper [28] does not refer to the option to delete the original record after having created a certified copy based on a validated process.
- The EMA requires compliance with Directive 95/46/EEC (protection of individuals with regard to the processing of personal data) [69]; however, the FDA does not refer to data protection in the Guidance for Industry [27].
- FDA intends to inspect EHR systems for compliance to CFR 21 Part 11 [27]. EMA considers EHRs containing source data to be in scope of the EMA Reflection Paper on Electronic Source Data [28].

This list is not complete and each organization needs to evaluate and identify applicable requirements based on their needs.

Further guidance in this Chapter is orientated towards what is perceived as the stricter requirements from the FDA and EMA documents. For example, in the case of EHR systems, the EMA requirements are followed when applying this Guide to eSource data. This enables compliance to both the FDA and EMA regulations.

In cases where the sponsor and investigator are the same entity, the requirements concerning control over source data may not be applicable.

To evaluate the risks the following EDC scenarios will be used:

Direct Entry of Data Into the eCRF

For data elements that are obtained and entered into the eCRF during a subject visit, the eCRF is the source. This includes any data elements entered that are assessments, e.g., of a CT scan image. The most significant risks to the data integrity are that data is not entered in a timely manner (not Contemporaneous), and that human errors occur during data entry (not Accurate).

A significant number of investigators participate in clinical studies in addition to or as part of their normal work as medical doctors in hospitals or practices. Emergencies or other duties might keep investigators from entering data accurately and/or in a timely manner. Not entering data in a timely manner, however, can lead to inaccurate and incomplete data.

Automatic Transmission of Data from Devices or Instruments Directly to the eCRF

If data originates from a device or instrument and the device or instrument generates a raw data file, then that raw data file plus the associated metadata are the source data. Even if that device or instrument is directly interfaced (and validated) with an eCRF, then the eCRF only contains a transcript of the source data. These setups are often found in early phase units or hospitals.

Also, if the device or instrument is interfaced in a validated way with an EHR system that in turn is interfaced with the eCRF, the device or instrument is the source of the data, unless the raw data file and metadata are immediately stored into the EHR.

Data integrity can be endangered if the interface can be (in parts) controlled by the end user. For example, if the transmission of data to the EHR or eCRF requires a manual trigger/intervention, data might not be transmitted at all or only part of the data is transmitted.

Transcription of Data from Paper or Electronic Sources to the eCRF

Especially for smaller sites and smaller clinical studies, it may not be feasible to implement and validate interfaces between the EHR or laboratory systems to the EDC. In such cases data is often manually transcribed from the EHR or laboratory system to the EDC, either by direct readout or intermediate paper. From a data integrity perspective, such approaches are no different than a study recorded on paper CRFs. For these data elements, the electronic or paper documents from which the data elements are transcribed are the source and must be maintained at the clinical site.

The most significant risks to data integrity are that data is not entered in a timely manner (not Contemporaneous) and human errors occur during the data entry (not Accurate). Data entry errors can be mitigated by appropriate edit checks in the eCRF. If data is transcribed from paper records the data integrity aspect of legibility is also a concern.

In the case that the generating instrument does not permanently store the data, the entry of the readout needs to be recorded directly into the EHR or EDC (contemporaneously, and with a double data entry control step). In that case, the EHR or EDC contains the source data.

If the readout is first written on paper, then the paper is the source. An example is a thermometer without interfaces that stores the last 10 temperature measurements. Given the double data entry control, it is not necessary to file the thermometer in the TMF after 10 measurements.

Direct Transmission of Data from the EHR to the eCRF

EHR systems that are interfaced with eCRFs can transmit data automatically to the eCRF. Data elements can be entered directly into the eCRF or can be transmitted by instruments or devices (see above). In both scenarios, the source of the data is the EHR System.

As interfaces to the eCRF often include algorithms to ensure that only appropriate data elements are selected, the correct design and implementation of these algorithms and interfaces is of key importance to data integrity.

Transmission of Data from Patient/Subject-reported Outcome Instruments to the eCRF

When an ePRO instrument is used by a subject to record and transmit data elements directly to the eCRF, the eCRF is the source. If the ePRO device transmits the data to a technology service provider database before it is included in the eCRF, the service provider database is the source. In this scenario, the ePRO device and software used are elements that can negatively influence data integrity.

In this context, it is worth noting that dedicated ePRO devices might be replaced by smartphone apps that will be executed on the smartphone of the subject in a BYOD design. These smartphones are technically versatile and significantly less controlled than dedicated ePRO devices and more subject to, e.g., virus attacks or modifications like jailbreaks.

More scenarios and guidance for the usage and integration of EHR systems can be found in the CDISC Electronic Source Data Interchange (eSDI) Group “Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials” [23].

To minimize the risks to data integrity, extensive, validated edit checks should be implemented that ensure the accuracy and completeness of the data. For critical data elements, this should be supported by SDV by a CRA during an on-site visit as well as through ongoing remote-monitoring activities.

To optimally support such monitoring activities, the involved systems should capture in an audit trail relevant metadata, like date and time of data entry and the identity of the user performing the entry. The systems should provide tools and reports that enable efficient and effective consistency and integrity checks that include the metadata, e.g., the data in the audit trail.

Appropriate validation and ongoing change control for these systems is a must. In addition, appropriate training and open communication between all parties (subject, investigator and study team, CRO, and sponsor) will further reduce the risks for data integrity.

6.6 Data Integrity in Computerized Systems Used in Clinical Trials: Audit Trails and Audit Trail Reviews

The basic, technological, definition of an audit trail is that of a log or table that contains metadata concerning when and by whom data has been originally entered, changed, or deleted [4, 8].

Also, the original values need to be visible, and audit trails need to be protected from being modified or disabled. They contain important metadata that needs to be maintained through the different interface transfers between systems, together with the data they describe.

While EMA Annex 11 [26] also demands that reasons for relevant changes and deletions are entered, 21 CFR Part 11 [8] does not.

In some cases, audit trails have been implemented as a log file to be written to in the background of a system and to be accessed only when requested during an inspection or special investigation.

On a process level, audit trails enable a review that determines if data is attributable and contemporaneous.

In order to serve this purpose, audit trails need to be seen in the context of the data life cycle, especially the processing and use steps.

Like in the paper world, when Good Documentation Practices are followed, any changes and deletions should be easily visible and understandable to anybody who reviews the data, either for approval or decision-making purposes. In order to enable this, audit trails should capture the reason for change or deletion of critical data.

Audit trails and their reviews should be seen as an internal control tool for the data, and not as an imposed regulatory requirement.

When considering audit trail reviews, it is useful to distinguish between the in-process audit trail review and the investigational audit trail review.

6.6.1 *In-process Audit Trail Review*

In-process audit trail reviews are performed by normal users of a computerized system as part of the normal business process. Systems need to be designed so that the audit trail information relevant to data being reviewed or used is visible on screen or easily obtainable, e.g., by clicking on a symbol next to the data itself. In addition, the approach to performing these reviews should be risk-based, as in the paper world.

An example of an in-process audit trail review is the review by sponsor staff of data entered into an electronic patient diary by the study subjects. Typical risks here are the insufficient control of the data entry, as it may be performed by clinical site staff (instead of the subjects), or the later updating of entered values by site staff during site visits, so that more subjects match the inclusion criteria.

As risk mitigation measures, sponsor staff should not only review the entered data, but also the dates and times when data has been entered. If data for all subjects at a specific site has been entered during the same time interval every day, with the same time lag between the different entries, then this could be an indication of data entry by site staff. Similarly, any occasion where a subject had first been classified as excluded and later, by a data change, became included should be more carefully reviewed than other subject data, e.g., by SDV.

In order to enable efficient in-process audit trail reviews, a thorough risk assessment of the different data types and the business process steps needs to be conducted to identify areas where in-process reviews should be performed.

For example, an automated and validated interface that runs between a CTMS and an EDC system usually does not require an in-process review of the associated audit trail information. On the other hand, changes of data in an EDC leading to the inclusion of a previously excluded subject probably should trigger an in-process review.

Also, the system should be designed in a way that it supports such reviews, either:

- By showing audit trail data on the same screen as the data itself
- By flagging updated data
- By sending alerts pointing out risky changes
- By providing easy-to-run, specifically-designed audit trail reports

For instance, an EDC could be designed so that during the review of a subject's eCRF data, the principal investigator can see all changes and deletions of data related to the subject on the same page, including the reasons. By this method, the principal investigator has the full picture of the data history before approving the subject's data without the need to run an extra report.

In-process audit trail reviews should be documented in the same way in which data reviews are documented, and should be described just as in the use procedures corresponding to the system.

On a maintenance process level, in-process audit trail reviews should also be integrated into the periodic user account review process, for example, to scan for any occasions where a normal user was given administrator rights for a short period of time.

Another type of in-process audit trail review should be performed as part of routine system maintenance by IT administrators. These should include checks as to whether or not the audit trail is still functional and has never been disabled, and if the system clocks used are working correctly. This can also cover a review of back end changes, which are typically not logged in application layer audit trails but may be recorded at the database level.

As with any risk-based activities, it can also be determined for a specific system that no in-process audit trail reviews are needed. In such cases, a risk assessment should document the justification for that conclusion.

6.6.2 *Investigational Audit Trail Review*

Investigational audit trail reviews, on the other hand, are triggered ad hoc as a result of findings during the in-process reviews or by other incidents. These reviews typically require searches and reports on the existing audit trail (and therefore assistance by an IT administrator of the system) to investigate data and time frames of particular interest.

For example, during the user account audit trail review it was found that a normal user of the pharmacovigilance database had been given administrator rights for a short period of time. An investigational review of changes and deletions to AE case data made by this user during that time period should be performed.

6.7 Data Integrity in Integrated eClinical Platforms: Dataflow and End-To-End Validation

Even if every system for every involved partner has been validated to commonly agreed standards and processes, it may still not be enough to ensure the integrity of data for a clinical trial.

The remaining risk results from the fact that the data is not just exchanged between two systems. Some of the data flows through multiple systems, at multiple partners.

The individual teams responsible for a system are aware of the immediate systems or partners with which they exchange data; however, most of the time, they are unaware of any further handovers or data transfers. For example, a change in System A, or the processes applicable to System A, may not have an effect on the directly-interfaced System B; but it may affect System C, which is interfaced with System B.

The data integrity within a platform needs to be ensured by various controls and measures. Fundamentally, a data life cycle needs to be defined and enforced with clear concepts for data ownership and data custody, and covers the life of the data from initial generation through destruction (see Section 6.4 Data Life Cycle). This requires a documented description of the eClinical Platform including all systems used as well as the dataflows for relevant data.

An end-to-end validation of critical dataflows through the eClinical Platform that also considers the processes for (documented) handovers of data and the transfer of data ownership/custody would support the protection of data integrity in eClinical Platforms.

For more information on eClinical Platforms, see Chapter 7.

6.8 Data Integrity for Electronic Documents Used in Clinical Trials: Electronic Signatures and Digital Signatures

Even though the regulations specifically enforce signatures only for a small number of key documents, e.g., the study protocol, it is industry best practice to sign a significant amount of the data or documents generated during a clinical study to ensure appropriate release and versioning of data as well as establishing appropriate accountability.

All signatures specified in the GCP-relevant SOPs of an organization should comply with regulatory expectations. ICH E6(R2) names the “essential documents for the conduct of a clinical trial.” [5] These documents should be signed and the signatures can be applied manually on paper, as an electronic signature in a system or as a digital signature.

If these documents are signed electronically, the electronic signature (that may be established e.g., by re-entry of username and password) is often sufficient. However, country-specific laws and regulations may require a digital or certified signature on specific clinical trial documents (e.g., informed consent forms have to be dated and individually signed in Germany).

The large number of parties in the conduct of a clinical study often makes it very difficult to collect all signatures on paper. A robust tracking system for all data and documents is needed that requires a significant amount of mailing of paper documents. This could result in signatures being applied to incorrect versions of documents or data.

Furthermore, processes for the appropriate archiving of signed versions must be in place. This is especially difficult if signed documents are scanned and emailed to “approve” documents and the paper original is collected later. In such scenarios, additional processes must be established to ensure:

- All scanned and emailed signed documents are also collected in paper
- All evidence is archived (the emails with the signed documents) to demonstrate that approval was given in a timely manner

Because such processes create significant additional overhead, most organizations use electronic signatures; however, approvals via email with or without scanned signatures are still quite common, especially for documents requiring approvals from more than one party (like study-specific validation documents).

Simple electronic signatures based on reauthentication of the user but do not use keys or certificates are well established within the industry; although the high degree of outsourcing causes some risks here too.

Since electronic signatures are only valid within the system in which they have been applied, robust processes must be in place for managing access to this system for multiple parties. For example, if documents are signed in an electronic DMS hosted and operated by a CRO, the following aspects should be addressed and appropriate processes put in place:

- Verification of the identity of the users
 - How to verify the identity of a user outside of the CRO?
- Provision of appropriate access rights for users
 - How to limit access to the data for users outside of the CRO?
 - How to secure data that is accessed from outside of the CRO organization?
- Timely termination of user access
 - How to terminate access to the data in a timely manner for users outside the CRO if they are leaving the partner organization?

Data integrity may be at risk through inappropriate access and potential data manipulation if these aspects are not addressed. In systems that are provided to, and used by, sites and investigators, e.g., EDC systems, the electronic signatures data integrity risks must be carefully evaluated and appropriate controls implemented.

If multiple parties are involved in the processing of electronically-signed records, it is often required to transfer this data across organizations. Electronic signatures are no longer verifiable when the data are exported out of the system in which they have been signed. If there are no additional controls in place (e.g., a process to digitally sign the data export), the validity of signatures can only be verified in the system in which the data has been signed.

Attention must be given to the security of data during the transmission/transport from one party to the other to avoid data loss or manipulation. Data transports, retention, archiving etc. should be considered in the contractual agreements between CROs and sponsors as well as in the validation of the system containing data to be transferred. Often digital signatures are used to safeguard data during transmission/transport.

An appropriate digital signature based upon cryptographic methods of originator authentication as defined for open systems in 21 CFR Part 11 could be used to mitigate the risks motioned above [8]. Digital signatures can provide or ensure:

- Authentication of the signatory as a single, unique identity is tightly bound to the digital signature
- Integrity of the data signed, as any change in the data invalidates the signature
- Non-repudiation of origin

A properly implemented digital signature solution will mitigate most of the data integrity risks outlined. Additionally, the certificate servers need to be visible to all involved parties, and not only in the intranet of the sponsor company.

If digital signatures are not used, procedural controls should be established, including collecting, tracking, and archiving paper signatures. If necessary, a process for creating a certified copy of the signed documented needs to be instituted so that an electronic copy can be stored as part of global inspection readiness.

6.9 Data Integrity for Electronic Documents Used in Clinical Trials: Certified Copy of Original Documents (Source Documents)

Frequently, electronic copies of (source) documents need to be created to:

- Establish global audit and inspection readiness
- Enable efficient electronic archiving

In some cases, this may encompass destroying the paper original after the electronic copy has been generated.

Source documents are regulated and require the creation of a certified copy if these copies will be used in lieu of the original.

The FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations [24] defines a certified copy as a copy of “original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.”

This requirement is best addressed by:

- Establishing a robust process for the digitalization and verification
- Using adequate hardware/software
- Validating the system and process including risk analysis and quality control

Moreover, any process to create a certified copy must consider the data integrity aspects for **Completeness** (is all information captured?) and **Legibility** (can all information be read?).

Evident risks for **Completeness**:

- Are all pages scanned?
- Is any information missing, e.g., on the back of pages?

Evident risks for **Legibility**:

- Can all the information be read?
- If Optical Character Recognition (OCR) is used, is the processed text accurate? (The use of OCR is discouraged.)
- Has there been any information captured by non-standard means, e.g., highlighter, and are they visible in the copy?

The assessment of the quality of the source documents is critical for the risk assessment of the overall digitalization process. In general, the poorer the quality of the source, the higher the requirements for the overall digitalization system, and the larger the sample size that needs to be checked in quality control.

Important aspects in the quality assessment of the source documents are:

- Quality of paper (office paper versus carbonless forms)
- Color (paper or pen) or black and white
- Pictures
- Special characters
- Handwritten notes etc.
- Availability of paginations and Table of Contents

The methods for the digitalization and the required quality control checks including the parameters for the risk-based approach should be documented in an SOP. This should include the classification features, the scanning parameters to be used, and the quality controls. The documentation of the checks can be done by electronic signature on each checked document.

While it may be acceptable to limit the quality control for high-quality source documents (e.g., normal DIN A4 office paper, 80 g, black/white text, no pictures and no special characters in the text, paginated) to 1% of the digitized documents, for poor quality source documents it may be necessary to perform a 100% check of the output.

In addition to page-by-page verification between the source document and the digital copy, checks should be performed for overall completeness, for instance, confirming the correct number of pages in the digital copy.

These scenarios should be considered when developing the validation strategy for any computerized system used to create a certified copy. Additionally, the aspects of storage/archiving and access control must be considered, described, and possibly tested.

If appropriate processes and controls for creating a trustworthy certified copy are established, the destruction of the paper original may be possible. It could be argued that this is desirable because:

- A single (electronic) master record would be established that would be the basis for all further processing
- Tighter access controls can be established, e.g., to protect personal data or to protect the blind of trial
- Increased availability for authorized personnel
- Reduced space for storage
- Cost reduction

However, before the paper original is destroyed it is strongly recommended to review applicable local regulations.

6.10 Risk Identification for Data Integrity and Data Quality

The ICH E6(R2) Quality Management [5] is risk-based, composed of the steps for Critical Process and Data Identification, Risk Identification, Risk Evaluation, Risk Control, Risk Communication, Risk Review, and Risk Reporting.

A key foundation for ensuring data integrity, data quality (and of course subject safety) is the detailed risk identification of the business process, data, and computerized system. Many such risk analyses fall short because they are often performed by IT and validation staff with only a specific computerized system in scope. Process aspects are often neglected.

In order to conduct a risk assessment that serves to identify risk mitigation actions so that ultimately the future business process enables and guarantees data integrity, the risk analysis needs to be performed by cross functional teams. It is especially important to include experts from the business process who will use the process, data, and computerized system.

The most important task is to identify all potential risks. A big challenge is that the “elephant in the room” is not documented; therefore, an open, brainstorming-like atmosphere can help. The following list contains points worth considering:

1. Consider all five system components (Hardware, Software, Processes, People, Documentation)
2. Walk along the data life cycle and all dataflows
3. Which business processes will use a specific computerized system?
4. Walk along all business processes

5. Classify data in system: high, medium, or low risk. Which data needs an audit trail? Which data needs to be reviewed for decisions, and which data needs an audit trail review for decision making? Consider data, metadata, and system data (also user accounts, administrator accounts, database and operating-system administrator accounts)
6. Consider all interfaces and manual data inputs/outputs, and manual data transfers
7. Along the business process and dataflow, in which systems or locations is data stored (including temporary storage during transfer)?
8. Consider the impact of the change or data migration on the business process
9. What experiences could be addressed from the current system and its issue log and CAPA files (for system upgrades/changes)?
10. How are changes in hosting location and potential legal implications managed?
11. How is decommissioning managed?
12. Who is the owner of the business process? How many teams are using it? Is a more refined governance structure needed?
13. How is the relationship to the vendor or hosting provider defined?
14. Consider cultural factors, both company-specific and country-specific. Where does the country in which the process takes place rank on the Transparency International scale [70]?

A risk analysis needs to be performed early in a project so that risk mitigation can be implemented early in the process and system design phase. Also, the risk assessment should be managed as a live document that is regularly reviewed and updated, even during the use phase of the system.

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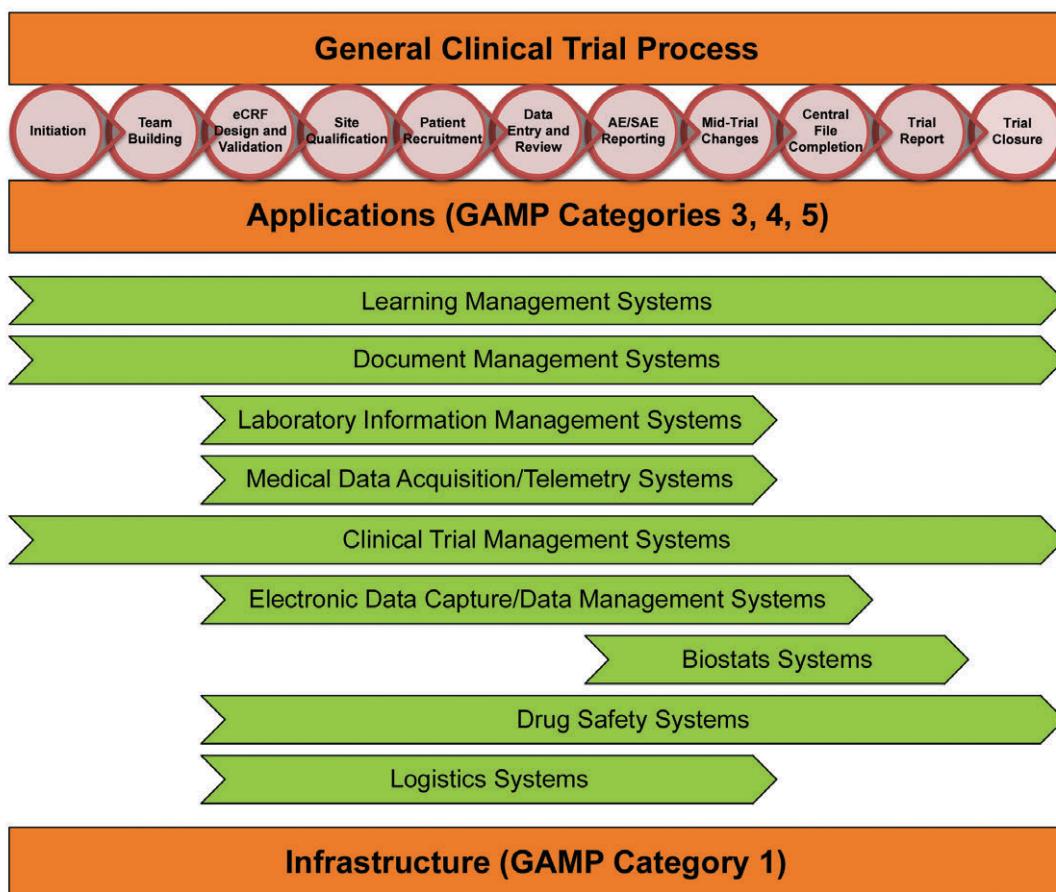
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7 Interfaces and Dataflows through Different Systems (eClinical Platforms/Architectures)

To enable efficient trial setups, especially in CROs and larger pharmaceutical companies, eClinical solutions have to be built from various specific systems and tools that then need to exchange data, and are often connected via interfaces (see Figure 7.1).

Figure 7.1: Mapping of Sample Systems to the Clinical Process



The need to ensure data integrity through the life cycle of a clinical study, and across all involved systems, is of paramount importance as inconsistent, incorrect, or corrupt data could endanger the safety of subjects. Also, the integrity of data used in any submission is an end unto itself.

For the purpose of this Guide, an eClinical Platform is defined as an existing environment of integrated computerized systems that can be adapted to support the conduct of a clinical study by utilizing existing, validated functionality and processes. Typical platforms include EDC, CTMS, eTMF, statistical systems as well as safety systems and others. Individual components of the eClinical Platform may require setup or configuration to meet the requirements of each clinical study.

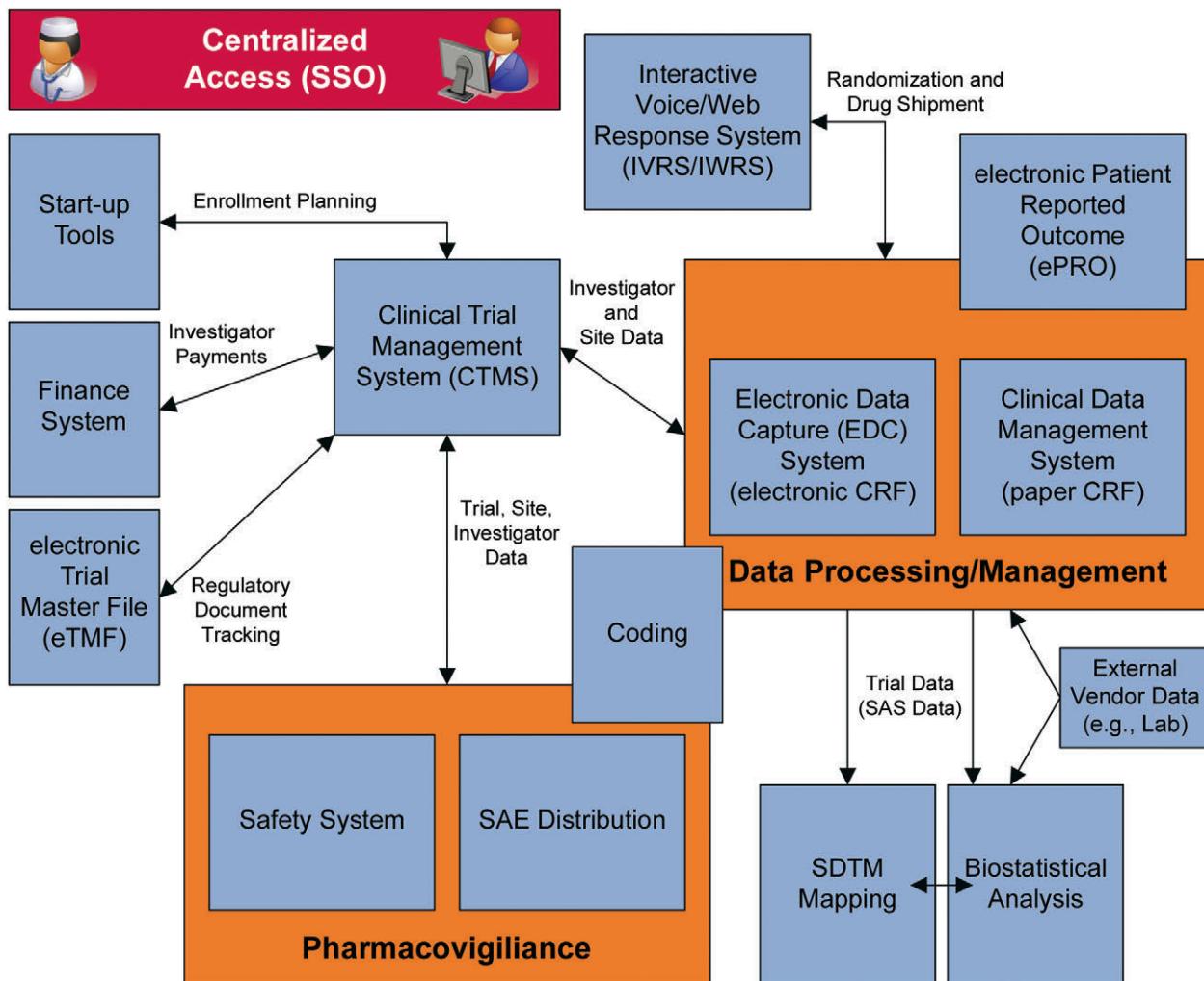
Not all clinical studies will need all systems to be part of an eClinical Platform (e.g., an open-label trial does not require systems that support blinding of trials). For instance, a Phase I trial may require different systems than a Phase IV trial. A Phase I trial may not require an expensive, complex, multilingual, and web-based EDC system, as Phase I trials are often conducted in only one location with very few users and subjects. Other examples could be a subject recruitment database or a barcode reader that may not be necessary in a Phase IV trial.

Additionally, some systems (e.g., CTMS) will collect and process data from all clinical studies conducted by the organization without further customization while others (e.g., EDC system) may need to be set up and configured for each trial based on the protocol requirements.

A further aspect that needs to be considered is the potential outsourcing of activities and the usage of SaaS offerings. The resulting eClinical Platform might span multiple organizations (e.g., the sponsor of the trial), one or more CROs and SaaS vendors (e.g., for an EDC system) and could even include EHR systems at the investigator sites or LIMS at the laboratories used.

A generic example of an eClinical Platform is provided in Figure 7.2.

Figure 7.2: Example of a Generic eClinical Platform



Considering all of these aspects, it becomes obvious that data integrity cannot be ensured by the validation of the individual systems and their point-to-point interfaces alone. A more holistic approach towards validation including relevant processes, data, and quality management is necessary because those systems are acting together across corporate borders and controlled by different quality systems. Similar to validating individual systems following a risk-based approach, the risks of the eClinical Platform must be identified, assessed, and adequately addressed.

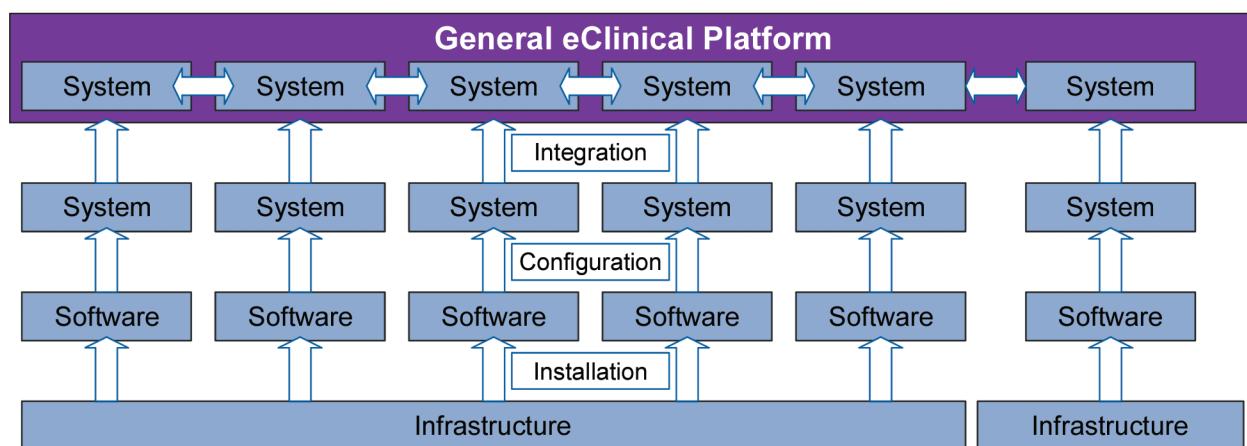
7.1 Generic eClinical Platforms versus Trial-Specific eClinical Platforms

As it would be inefficient to build a full eClinical Platform for every trial, establishing a generic eClinical Platform based on the individual GCP systems is required.

A generic eClinical Platform consists of all potentially required systems for the conduct of a clinical study. These are typically connected via numerous interfaces. Basic functionality and configuration that is required for the majority of clinical studies are included and validated following a risk-based approach.

This generic eClinical Platform also includes all SaaS offerings and systems from strategic partners like CROs that are frequently used for the conduct of clinical studies. The necessary transfer of data between the clinical study site, CRO, and sponsor adds significantly to the complexity of the platform.

Figure 7.3: Building a Generic eClinical Platform

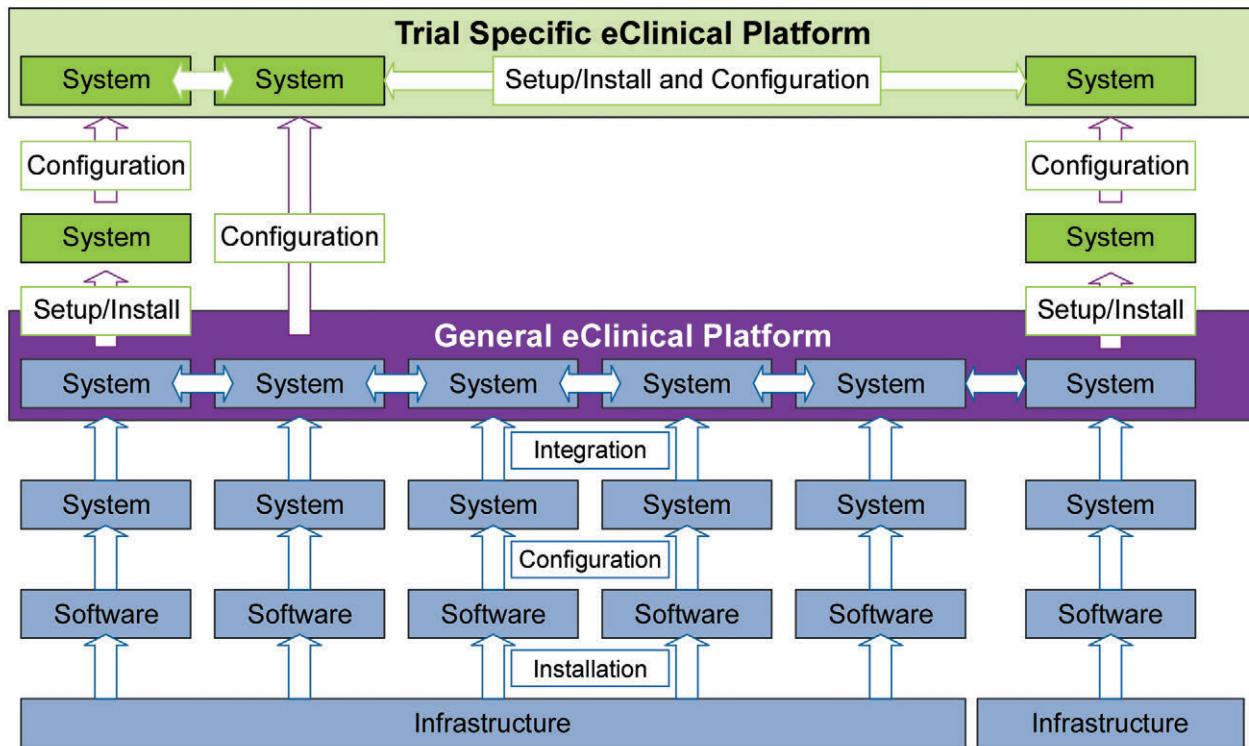


The generic eClinical Platform provides the validated baseline for any trial-specific platform and additional validation activities. This validated baseline enables organizations to establish a trial-specific eClinical Platform (Figure 7.4) in a timely manner as only the aspects that differ from the baseline need to be validated for the setup and configuration of the trial.

Depending on the type and complexity of the clinical study, the trial-specific eClinical Platform may simply contain a subset of the systems offered by the generic eClinical Platform and includes trial-specific setups and configurations of these systems. Furthermore, trial-specific requirements may entail the development, setup and/or configuration of trial-specific interfaces within the organization and/or between organizations.

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Figure 7.4: Creating a Trial-Specific eClinical Platform



7.2 Interfaces

7.2.1 Technical Aspects

Interfaces may be between internal systems or reach across multiple organizations. The setup often includes systems from the sponsor, CRO(s), various suppliers including EDC providers, laboratories, ePRO providers, logistics, and others. Additionally, systems at the investigator site, like EHR systems, may be included in the eClinical solution.

Interfaces as part of eClinical Platforms can be categorized as:

- Non-Configured Interfaces
 - These interfaces **do not** require any configuration and usually transfer data that are processed as part of every trial. These interfaces would typically be validated as part of the generic eClinical Platform validation.

Example: CTMS to safety system integrations
- Configurable Interfaces
 - These interfaces **do** require significant configuration and usually transfer data that is processed as part of every trial as well as trial-specific data. The validation of these interfaces is often split between the generic eClinical Platform validation (e.g., validation on system level) and the trial-specific eClinical Platform validation (e.g., validation on trial level).

Example: EDC system to CTMS integrations or EDC system to IVRS/IWRS/IRT

- Trial-Specific Custom-Built Interfaces
 - These interfaces are custom-built to address a very specific need of the trial, or group of trials, and are unlikely to be used again for future trials. The validation of these interfaces is typically conducted during the trial-specific eClinical Platform validation.

Example: EDC system to ePRO integrations or partly-manual interfaces (e.g., upload of laboratory results)

A categorization that defines the responsible party for operation and maintenance of a system is also helpful:

- Interfaces between systems of the same organization
- Interfaces between trusted partners
- Interfaces between one-time/first-time partners

While integrated systems of the same organization are usually very well controlled, the setup, operation, and maintenance of interfaces between different organizations are more challenging. This requires well-established communication and sound contractual arrangements to address potential differences in the validation approach and to provide agreement on standards to be used. Such arrangements are usually made with trusted partners that are considered to be reliable, trustworthy, and used and audited several times. Typically, these partners have the status of a preferred supplier/vendor and there is a well-established Service Level Agreement (SLA) in place.

7.2.2 Organizational Aspects: Outsourcing

Ensuring the integrity of data collected and managed by a computerized system is essential to support the evaluation of the investigational product and ultimately protect subject safety. As stated in ICH E6(R1) *Guideline for Good Clinical Practice* [13], “the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor” therefore, the sponsor must establish adequate quality oversight.

The current trend of pharmaceutical companies to outsource significant parts of their clinical study activities and IT systems often leads to a complex eClinical Platform involving several partners, one or more CROs, and multiple IT providers.

The EMA Reflection Paper [28] discusses outsourcing of the eClinical Platform to a third party with strict controls over sponsor access. This could help the sponsor demonstrate that they do not have exclusive control over source documents.

To ensure the essential quality aspects of a clinical study, the foundation of the cooperation between these parties must be laid out in contracts and Master Service Agreements (MSA), Statements of Work (SOW), and similar legally-binding documents.

Incorporating basic quality, organization, and communication requirements into these documents is considered good practice. These expectations should include:

- Audit frequency or schedules
- Establishing steering committees/governance boards, etc.
- Expectations for metrics/Key Performance Indicators (KPI)
- Communication of issues
- Advance notifications for system changes and/or downtimes

- Direct access to partner systems and/or data
- Details of data transfer (e.g., security, frequency, technology, etc.), including all metadata in a processable form (relational database)
- Usage of electronic or digital signatures
- Details for protection of personal data
- Change control aspects for processes, systems, data, and trials
- Details of backup schedules and disaster recovery plans including availability requirements
- Management of user accounts, including identity verification and periodic reviews
- Upgrade/maintenance schedules
- Strict controls over sponsor access to independently-hosted data
- Training requirements, especially ensuring knowledge of health authority regulations
- Non-disclosure agreement(s)
- Escrow agreement
- Notification for subcontracting

It is recommended to include change control aspects in the contract/Master Service Agreement, as changes made to systems or processes are likely to break interfaces or to put data integrity at risk.

Change control should include mid-trial changes that mandate technical modifications, as it has been clearly demonstrated that protocol amendments and modification are the norm and not the exception [12].

Agreements should outline the types of system changes that must be communicated to the sponsor and which changes require approval prior to implementation.

Also, the use and validity of electronic signatures, when the data is transferred from one partner to another, needs to be carefully considered. It might be necessary to use digital signatures for some data elements to allow verification of the signature at any time.

Generally, open and honest communication between all partners is essential for the success of an eClinical Platform, and subsequently the success of the trials conducted; therefore, not only are contracted items crucial for data integrity throughout the entire trial life cycle, but also the contact between the responsible project's personnel.

Regular meetings (e.g., weekly, biweekly, etc.) during the trial life cycle are essential. Furthermore, the participation of all relevant parties including Business, IT, and Quality is vital as systems and trial setup are likely to change over time.

A good team, managed by project managers from the sponsor and the supplier(s), is a key factor for the success of the trial and maintaining data integrity. Another important aspect is for the supplier(s) to fully understand all of the regulations with which the sponsor must comply, and that they are a vital part in ensuring that compliance is maintained. This includes not only supporting audits and inspections by the supplier and/or regulators, but also the timely reporting of incidents to the sponsor. The criteria for incident reporting may be specified in the contract.

The protection of personal data and subject confidentiality as well as the blinding/unblinding of data pose additional challenges.

It must also be understood that the intellectual property of the involved partners must be protected, as some partners may be competitors in the same market. For example, a sponsor may work with several CROs or EDC providers. This should be considered throughout all communication channels when multiple parties are involved.

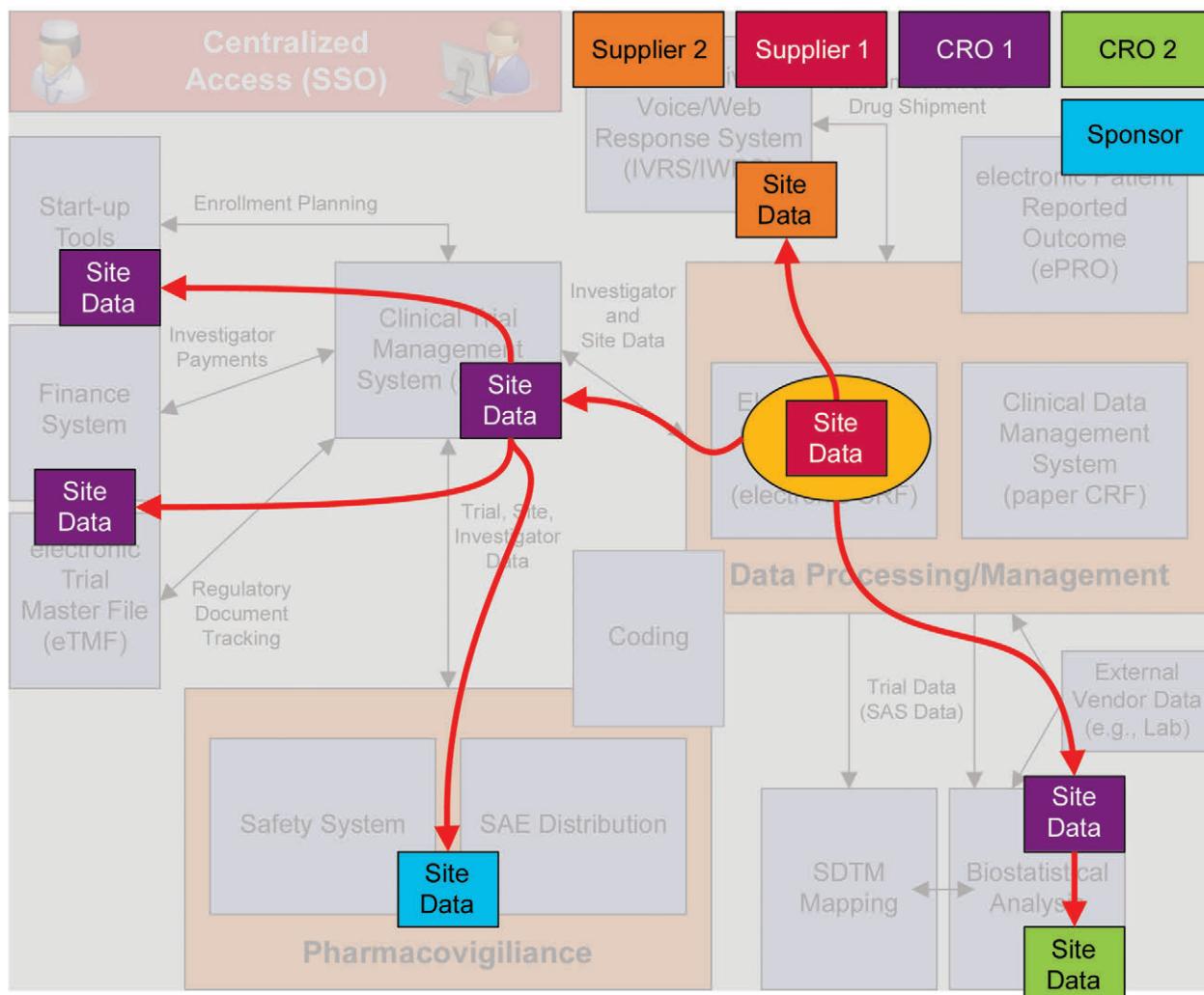
7.3 Dataflow and End-To-End Validation

Aristotle said: "The whole is more than the sum of its parts." [71]

In this context, even if every involved system for every involved partner has been validated to commonly agreed standards and processes, including clearly defined risk-based approaches, it may still not be enough to ensure the integrity of data.

The remaining risk results from the fact that the data is not just exchanged between two systems or two parties. Some of the data flows through multiple systems, at multiple partners, as shown in Figure 7.5.

Figure 7.5: Data Flows in eClinical Platforms



The individual teams responsible for a system are often aware of the immediate partners or systems with which they exchange data; however, most of the time, they are unaware of further handovers or data transfers. Therefore, a change in System A, or the processes applicable to System A, may not have an effect on the directly-interfaced System B; but it may have an effect on System C that is interfaced with System B.

Obviously, this could be avoided if every system would “read” the required data directly from the source; however, this might not be possible for either procedural and/or legal reasons.

An Example:

A trial startup tool provides site data (e.g., name, contact details, etc.) to the CTMS. At this point in time these sites have not been initiated, as they are imported into the CTMS as “ready for initiation”. Once the initiation is completed, the data is transferred to the EDC system triggering the sending of login details.

A change in the way the data is collected in the trial startup tool (e.g., fax numbers are no longer captured) may not have direct consequences in the CTMS (as the users employ other means of communication such as email); however, it could trigger problems in the EDC system (as it sends the user name via email but the initial password via fax).

Data that is often transferred in such ways include:

- Investigator data: often processed in CTMS, EDC, IRT and financial systems
- Site data: often processed in CTMS, EDC, IRT and trial startup tools
- Safety data: often processed in CTMS, EDC, and safety systems

As a consequence, data integrity is at risk. However, the integrity of the data could be established by end to end verification of the eClinical Platform.

This could be achieved by setting up every trial in a test environment of the full eClinical Platform. In this setup, all planned/proposed changes for the systems, or for the trial, could be tested prior to release to production in order to mitigate risk to data integrity; however, this is a rather costly approach.

Alternatively, if dataflow could be analyzed alongside the clinical processes, the risks associated with these dataflows could be determined. This would require a much more detailed analysis of the processes, data, and records than is typically done. Furthermore, it would require a Review Board able to carry out extensive impact and risk assessments for each change request and has sufficient organizational leverage to act upon identified risks.

It must be understood that these activities are not limited to automated data transfers. Quite often data are transferred at specific intervals or at specific project milestones by manual handovers. An example would be the handover of the locked database content from data management at a CRO to the sponsor for further analysis. This is often done via a manual upload to a secure FTP site.

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7.4 Validation in Different Organizations

Every interface can potentially endanger the data integrity of a trial; consequently, all interfaces and systems should be assessed and validated following the same standards. This is often very difficult to verify, achieve, or establish if the eClinical Platform involves systems validated by different organizations following their own standards and procedures.

Terminology is often used inconsistently across various parties, which produces additional challenges in communication. Mapping of the individual validation deliverables and terminology to *ISPE GAMP® 5* [3] can establish transparency and help identify gaps. This can be done as part of regular audits or as part of on-going communication between the involved organizations. The sponsor should ensure the oversight of any trial-related duties and functions carried out on its behalf, and the sponsor should document approval of any subcontracting of trial-related duties and functions by a CRO.

Sponsors may consider establishing a Quality Committee, with representatives from all strategic/preferred partners, to define requirements and develop a common approach. This committee may also ensure that all partners are aware of the most recent changes in relevant regulations. It is noteworthy that recent guidance released by the FDA explicitly states that the FDA does not intend to inspect EHR systems against the standards of 21 CFR Part 11 [27]. In contrast, the EMA sees electronic source data systems at clinical sites as being within the scope of their reflection paper [28].

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9 Appendix 2 – Glossary

9.1 Acronyms and Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ALCOA	Acceptable, Legible, Contemporaneous, Original, Accurate
ALCOA+	ALCOA, with the addition of Complete, Consistent, Enduring, Available
BR	Blinded Reading
BYOD	Bring your own Device
CAPA	Corrective and Preventive Action
CD	Compact Disc
CDASH	Clinical Data Acquisition Standard Harmonization
CDISC	Clinical Data Interchange Standards Consortium
CoA	Certificate of Analysis
CoC	Certificate of Compliance
COTS	Commercial Off-The-Shelf
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract/Clinical Research Organization
CSR	Clinical Study Report
CTD	Common Technical Document
CTMS	Clinical Trial Management System
CV	Curriculum Vitae
DICOM	Digital Imaging and Communications in Medicine
DMS	Document Management System
DSUR	Development Safety Update Report
DVD	Digital Video Disc
e	electronic (e.g., eCRF, eCTD, ePRO, eTMF)
EC	Ethics Committee
EDC	Electronic Data Capture
EDMS	Electronic Document Management System
EHR	Electronic Health Record
EMA	European Medicines Agency (EU)
EU	European Union
FDA	Food and Drug Administration (US)
FTP	File Transfer Protocol

GAMP®	Good Automated Manufacturing Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMP	Identification of Medicinal Products
IIT	Investigator Initiated Trial
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ISO	International Organization for Standardization
IT	Information Technology
ITIL®	Information Technology Infrastructure Library
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LIMS	Laboratory Information Management System
LMS	Learning Management System
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare (Japan)
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MKT	Mean Kinetic Temperature
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MSSO	Maintenance and Support Services Organization (ICH MedDRA)
NDA	New Drug Application
PACS	Picture Archiving and Communication System
PRO	Patient Reported Outcome
QA	Quality Assurance
QP	Qualified Person
RBM	Risk-Based Monitoring
RECIST	Response Evaluation Criteria in Solid Tumors
SaaS	Software as a Service

SAE	Serious Adverse Event
SAP®	Systems Applications and Products software
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SDV	Source Data Verification
sFTP	secure File Transfer Protocol
SOP	Standard Operating Procedure
SQL	Structured Query Language
SRA	Study Reference Architecture
SSA	Study Specific Architecture
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UAT	User Acceptance Testing
WHO	World Health Organization
XML	Extensible Markup Language

9.2 Definitions

Note: consult ICH E6(R2) [5] for definitions of clinical terms.

Audit Trail (FDA [40])

A process that captures details of information, such as additions, deletions, or alterations, in an electronic record without obscuring the original record. An audit trail facilitates the reconstruction of the course of such details relating to the electronic record.

Certified Copy (ICH E6(R2) [5])

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Data Entry (CDISC [72])

Human input of data into a structured, computerized format using an interface such as a keyboard, pen-based tablet, or voice recognition. NOTE: although data capture is often used synonymously, capture implies direct entry of original source data into an electronic record rather than transcription (entry) from paper source.

Data Life Cycle (MHRA [73])

All phases in the life of the data (including raw data) from initial generation and recording through processing (including analysis, transformation or migration), use, data retention, archive/retrieval and destruction.

Data Quality (CDISC [72])

A dimension of data contributing its trustworthiness and pertaining to accuracy, sensitivity, validity, and suitability to purpose. Key elements of data quality include attribution, legibility (decipherable, unambiguous), contemporaneity, originality (e.g., not duplicated), accuracy, precision, completeness, consistency (logical, not out of range), and those who have modified the data. NOTE: scientists may reasonably trust data that are accurate (high quality) that have also been reviewed by investigators and protected from unauthorized alteration (high integrity).

Data Storage (HL7® EHR-S FM Glossary of Terms 2010 [63], CDISC [72])

To maintain data by placing the data, or a copy of the data, onto an electronically accessible device for preservation (either in plain-text or encrypted format).

Digital Signature (21 CFR Part 11 [8])

An electronic signature, based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

Direct Entry (FDA [15])

Recording data where an electronic record is the original means of capturing the data. Examples are the keying by an individual of original observations into a system, or automatic recording by the system of the output of a balance that measures subject's body weight.

Edit Check (CDISC [72])

An auditable process, usually automated, of assessing the content of a data field against its expected logical, format, range, or other properties that is intended to reduce error.

Electronic Data Capture (EDC) (CDISC [72])

The process of collecting clinical study data into a permanent electronic form. NOTE: permanent in the context of these definitions implies that any changes made to the electronic data are recorded with an audit trail. EDC usually denotes manual entry of CRF data by transcription from source documents. The transcription is typically done by personnel at investigative sites.

Electronic Record (21 CFR Part 11.3(b)(6) [8], FDA [40])

Any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

eSource Data (*Electronic Source Data*) (CDISC [72])

Source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a clinical study. **Note:** “permanent” in the context of these definitions implies that any changes made to the electronic data are recorded via an audit trail.

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GxP Regulation (ISPE GAMP® 5 [3])

The underlying international pharmaceutical requirements, such as those set forth in the US FD&C Act, US PHS Act, FDA regulations, EU Directives, Japanese regulations, or other applicable legislation or regulations under which the company operates. These include but are not limited to:

- Good Manufacturing Practice (GMP) (pharmaceutical, including Active Pharmaceutical Ingredient (API))
- Good Clinical Practice (GCP)
- Good Laboratory Practice (GLP)
- Good Distribution Practice (GDP)
- Good Quality Practice (GQP)
- Good Pharmacovigilance Practice
- Medical Device Regulations
- Prescription Drug Marketing Act (PDMA)

Interface (ISPE Glossary [74] (ANSI/IEEE))

A shared boundary. To interact or communicate with another system component.

Metadata (MHRA [73])

Data that describe the attributes of other data, and provide context and meaning. Typically, these are data that describe the structure, data elements, inter-relationships and other characteristics of data. It also permits data to be attributable to an individual (or if automatically generated, to the original data source).

Mobile Applications (Mobile Apps) (FDA [40])

Software applications that can be executed (run) on a mobile platform (i.e., a handheld Commercial Off-The-Shelf (COTS) computing platform, with or without wireless connectivity) or a web-based software application that is tailored to a mobile platform but is executed on a server. An example includes electronic patient-reported outcomes (ePRO) applications on smart phones.

Mobile Technology (FDA [40])

Refers to portable electronic technology used in clinical investigations that allows for off-site and remote data capture directly from study participants and includes mobile platforms, mobile apps, wearable biosensors and other remote and ingestible sensors, and other portable and implantable electronic devices.

Original Record (MHRA [73])

Data as the file or format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record, e.g. original paper record of manual observation, or electronic raw data file from a computerised system.

Platform (FDA [40])

The hardware and software which must be present and functioning for an application program to run (perform) as intended. A platform includes, but is not limited to the operating system or executive software, communication software, microprocessor, network, input/output hardware, any generic software libraries, database management, user interface software, and the like.

Record (ISO 9000:2015 [75])

Document stating results achieved or providing evidence of activities performed.

Risk (ISO/IEC Guide 51:2014 [76])

Combination of probability of occurrence of harm and the severity of that harm.

Source Data (ICH E6(R2) [5])

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Wearable Biosensors (FDA [40])

Miniaturized sensors worn as on- or in-body accessories (e.g., watches, bracelets, clothing) that allow for continuous monitoring of physiological, biochemical, and motion signals for both diagnostic and monitoring applications. These wearable biosensors may be paired with mobile platforms (e.g., smart phones). Examples of wearable biosensors include accelerometers, activity trackers, wireless heart rate monitors, pulse oximetry sensors, and glucose sensors.

Validation of Computerized Systems (ICH E6(R2) [5])

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system.

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