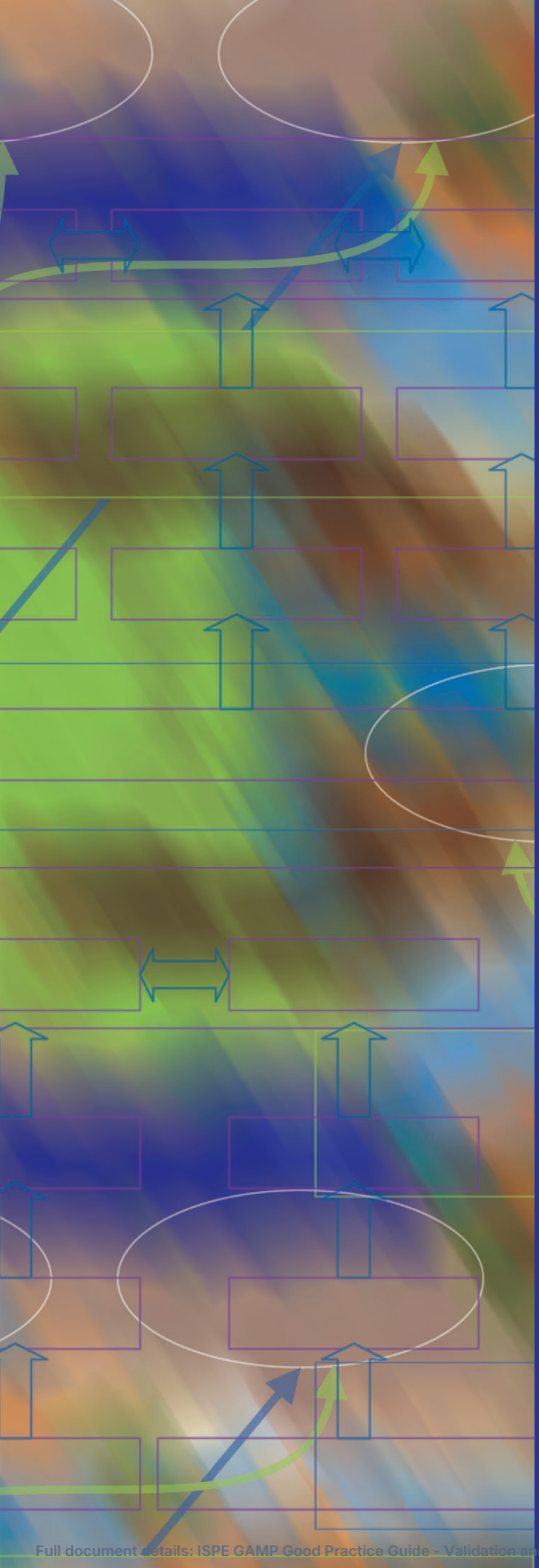


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Disclaimer:
This Guide is intended to provide a risk-based approach to validating diverse computerized GCP systems. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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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 Hamonisation (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).

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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.

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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 confidentially 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.

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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].

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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.

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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.

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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]

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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.

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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

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- 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.

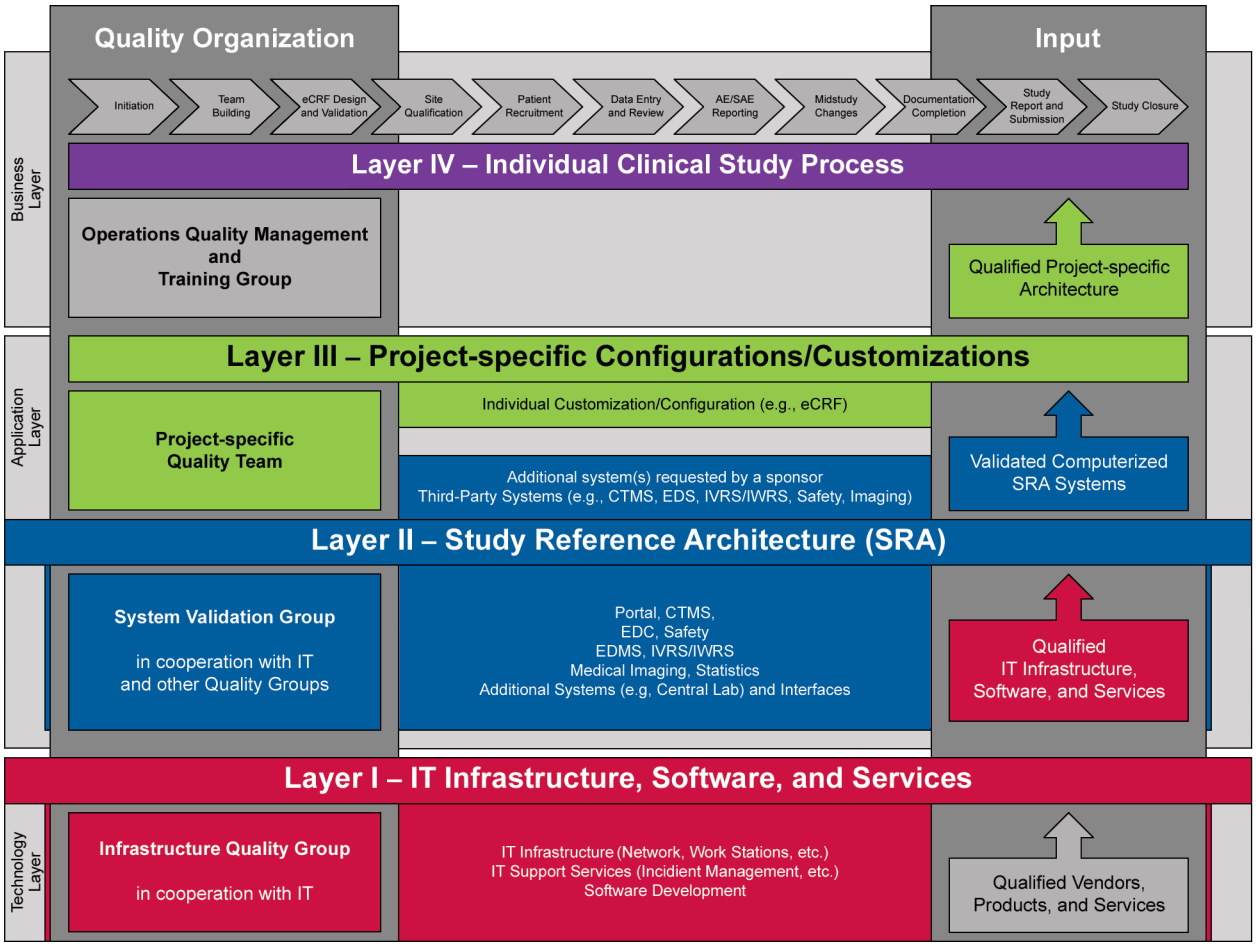
- **Underlying IT Infrastructure** building the Technology Layer – Layer I
- **Study Reference Architecture (SRA)** part of the Application Layer – Layer II

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- **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].

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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.

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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.

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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.

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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.

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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.

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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.

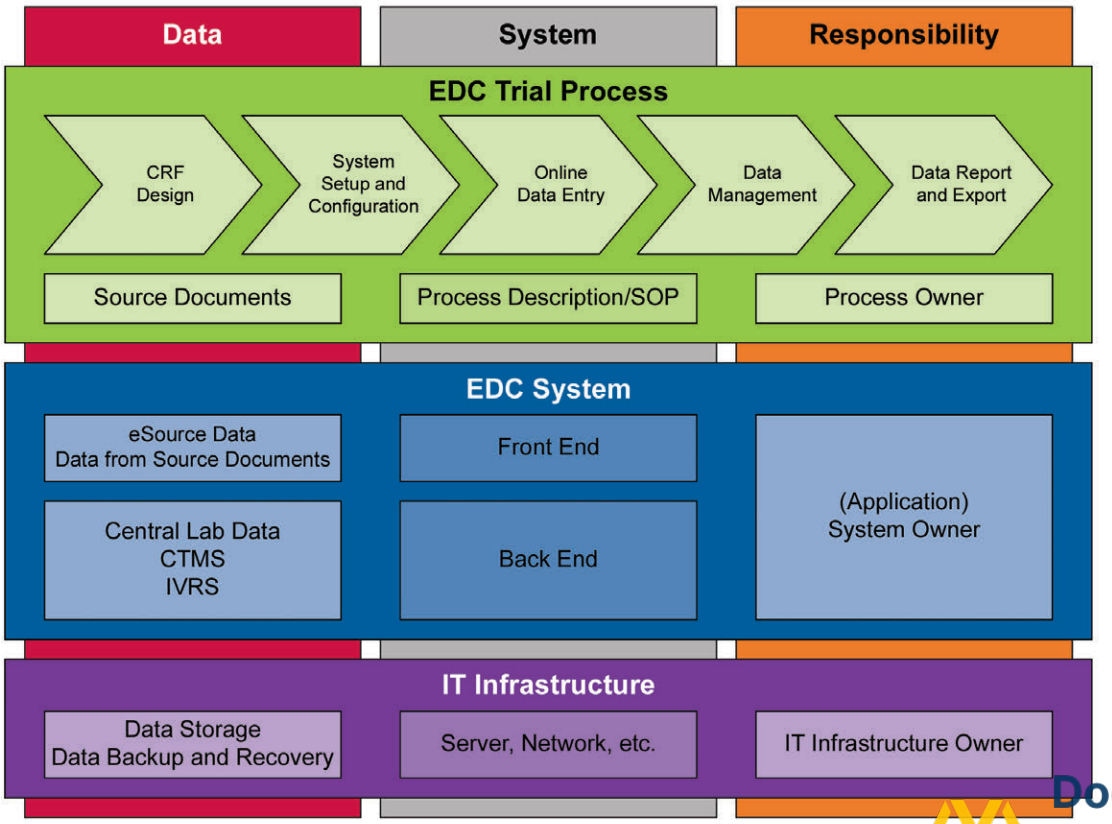
The trial-specific EDC setup is designed on the basis of a final trial-specific eCRF and contains the eCRF plus additional functionalities. The CRFs are created/adapted for each trial project based on the respective trial protocol and can contain complex calculations and data verification checks.

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



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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.

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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.

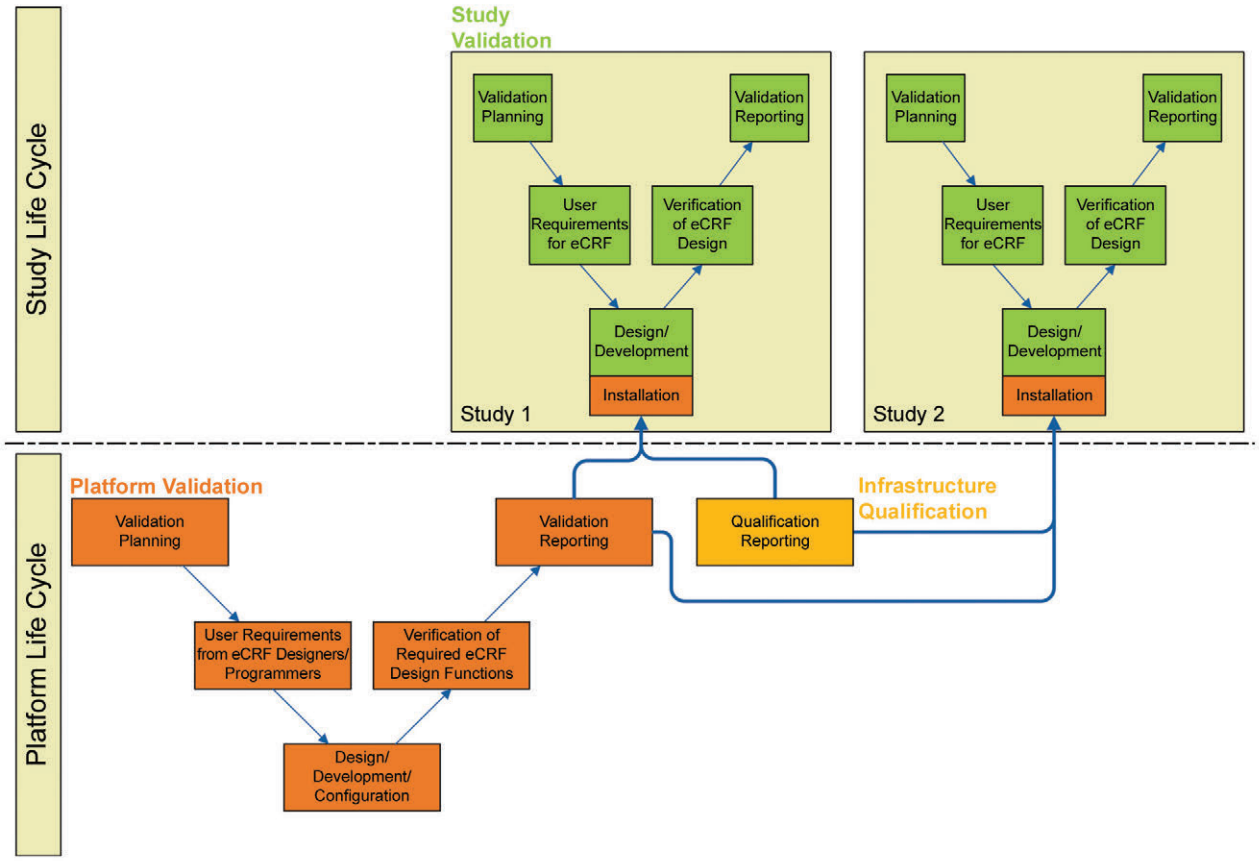
Whenever data is reviewed and approved, the reviewer/approver needs readable access to the changes and deletions of these data (audit trail) to allow further investigation and audit trail review when the integrity of a record is in question. For example, when a principal investigator reviews and approves 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.

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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).

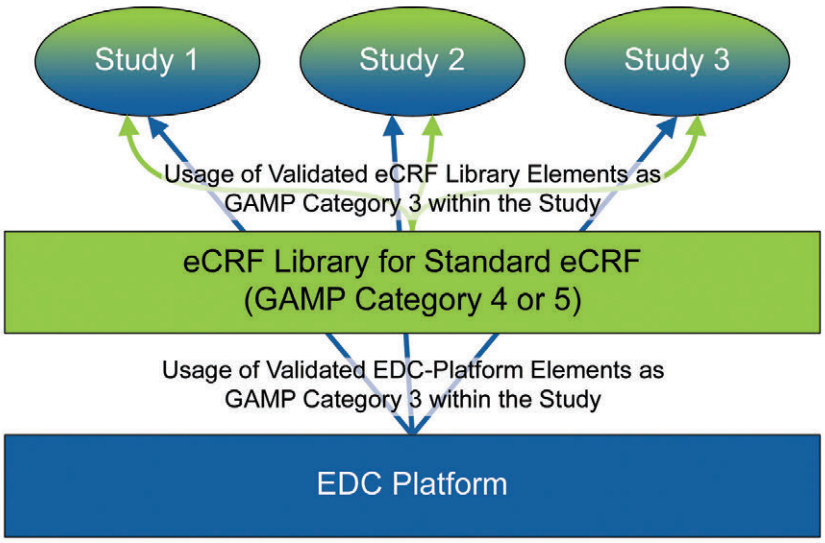
EDC systems are often supported by CRF library systems that are either COTS systems (GAMP Category 4) or custom developed (GAMP Category 5). Once these library systems are validated, they can store validated, versioned eCRFs. These eCRFs then can be reused with minimal effort, significantly reducing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

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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.

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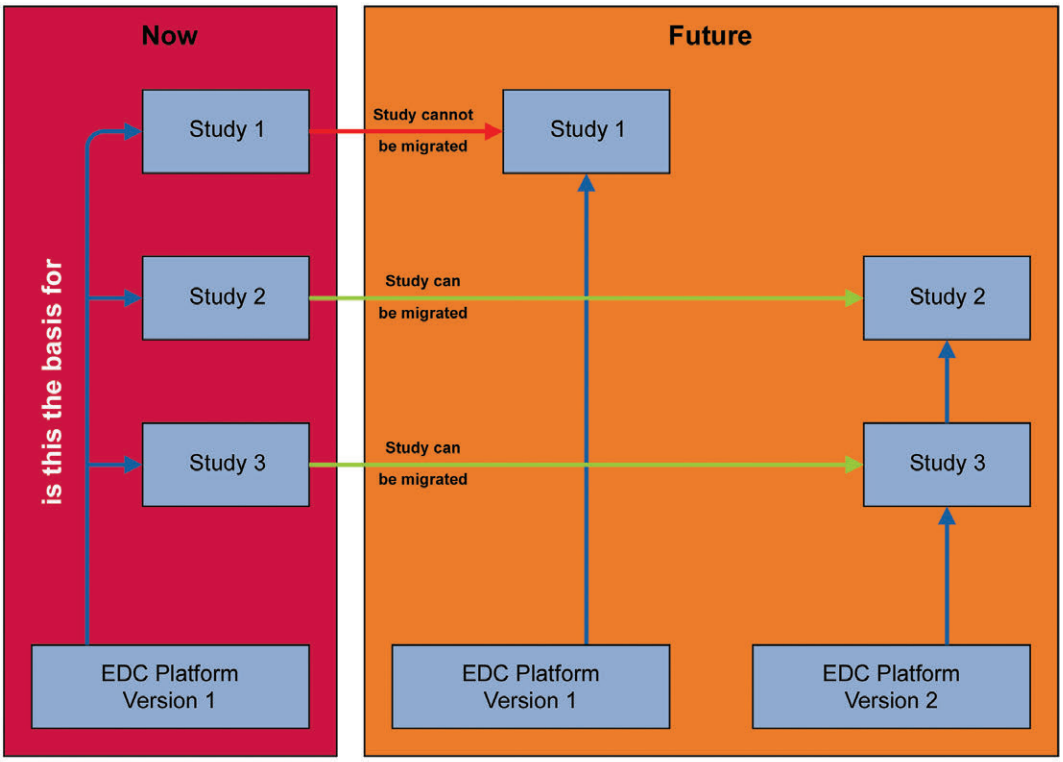
If the decision has been made to update the EDC platform an impact analysis must be conducted to consider:

- 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

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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.

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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.

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