

GOOD PRACTICE GUIDE:

Validation and Compliance of Computerized GCP Systems and Data

Good eClinical Practice



GOOD PRACTICE GUIDE:

Validation and Compliance of Computerized GCP Systems and Data

Good eClinical Practice

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.

Limitation of Liability

In no event shall ISPE or any of its affiliates, or the officers, directors, employees, members, or agents of each of them, or the authors, be liable for any damages of any kind, including without limitation any special, incidental, indirect, or consequential damages, whether or not advised of the possibility of such damages, and on any theory of liability whatsoever, arising out of or in connection with the use of this information.

© Copyright ISPE 2017. All rights reserved.

All rights reserved. No part of this document may be reproduced or copied in any form or by any means – graphic, electronic, or mechanical, including photocopying, taping, or information storage and retrieval systems – without written permission of ISPE.

All trademarks used are acknowledged.

ISBN 978-1-946964-03-8

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.

Acknowledgements

The Guide was produced by a Task Team led by Oliver Herrmann (Q-FINITY Quality Management, Germany) and Eric J. Staib (PRA Health Sciences, USA). The work was supported by the ISPE GAMP Community of Practice (CoP) R&D and Clinical Systems Special Interest Group (SIG).

Core Team

The following individuals took lead roles in the preparation of this Guide:

Jenny Gebhardt	Q-FINITY	Germany
Frank Henrichmann	PAREXEL International GmbH	Germany
Oliver Herrmann	Q-FINITY	Germany
Angelika Kellings	Universitätsklinikum Bonn – Studienzentrale SZB	Germany
Marina Mangold	Esculape	Germany
Yvonne Rollinger	OmniComm Europe GmbH	Germany
Eric J. Staib	PRA Health Sciences	USA
Maximilian Stroebe	GSK Vaccines	Netherlands
Dieter Wachtmann	PAREXEL International GmbH	Germany

Contributors and Reviewers

The Core Team wish to thank the following individuals for their valuable contribution during the preparation of this document.

Aneta Blazevska	AbbVie	Germany
Richard Chamberlain	ESC Inc.	USA
Jamie Colgin	Colgin Consulting, Inc	USA
Tamara Dehnhardt	B. Braun Melsungen AG	Germany
Ian Francis	Novartis Pharma AG	Switzerland
Ina Helm	Alcedis GmbH	Germany
Matt Jones	Boehringer Ingelheim	United Kingdom
Corinne Liabeuf	Johnson & Johnson	Switzerland
Sebastian Müller	Miltenyi Biotec GmbH	Germany
Nicola Parr	Janssen Cilag Ltd.	United Kingdom
Sarah Pickersgill	Celerion	France
David Stokes	Convalido Consulting Ltd.	United Kingdom
Teri Stokes	Cytel	USA
Olga Stoll	Bayer Consumer Care AG	Germany
Thanabalan Subramanian	Otsuka Pharmaceutical	United Kingdom
Lorrie Vuolo-Schuessler	GlaxoSmithKline	USA
Frank Woods	GlaxoSmithKline (retired)	United Kingdom

Regulatory Input and Review

Christa Färber	Trade and Industrial Agency of State of Lower Saxony – Agency Hanover	Germany
Jonathan Helfgott	Johns Hopkins University (former FDA)	USA
Gabriele Schwarz	German Federal Institute for Drugs and Medical Devices	Germany

Special Thanks

The Team would like to give particular thanks to Chris Clark (TenTenTen Consulting, UK), Chris Reid (Integrity Solutions, UK), Mike Rutherford (Eli Lilly and Company, USA), and Sion Wyn (Conformity Ltd., UK) for their efforts during the creation process of this Guide.

The Team Leads would like to express their grateful thanks to the many individuals and companies from around the world who reviewed and provided comments during the preparation of this Guide; although they are too numerous to list here, their input is greatly appreciated.

Company affiliations are as of the final draft of the Guide.



600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

www.ISPE.org

Table of Contents

1	Introduction	7
1.1	Purpose.....	8
2	Scope	9
2.1	Similarities and Differences between GMP and GCP Systems	9
3	Regulatory Overview	13
3.1	History.....	13
3.2	Regulations and Documents.....	16
4	Process Overview	17
4.1	The Project Nature of Clinical Studies	17
4.2	Stakeholders in Clinical Studies.....	18
4.3	Conducting a Clinical Study.....	18
4.4	Support through Computerized Systems	19
4.5	Validation Layer Model.....	19
5	Process Model.....	23
5.1	Process: Study Protocol and Submission for Approval.....	23
5.2	Process: Project and Clinical Study Management.....	24
5.3	Process: Electronic Data Capture System Life Cycle and Validation	29
5.4	Process: Electronic Patient Reported Outcome System Life Cycle and Validation	36
5.5	Process: Site/Partner Qualification	37
5.6	Process: Investigational Medicinal Product Management	43
5.7	Process: Subject Recruitment, Inclusion, and Randomization	53
5.8	Process: Data Aggregation and Review	57
5.9	Process: Severe Adverse Event Reporting.....	68
5.10	Process: Mid-Study Changes and Change Management.....	73
5.11	Process: Statistical Analysis and Programming.....	74
5.12	Process: Study Report, Study Closure, and Submission.....	76
5.13	Process: Quality Assurance and Quality Control	83
5.14	Process: Laboratory Analysis and Sample Logistics	86
6	Data Integrity.....	89
6.1	Definition.....	89
6.2	Risks	90
6.3	Data Ownership and Governance.....	91
6.4	Data Life Cycle.....	91
6.5	Data Integrity in Computerized Systems Used in Clinical Trials: electronic Source Data (eSource Data).....	92
6.6	Data Integrity in Computerized Systems Used in Clinical Trials: Audit Trails and Audit Trail Reviews	94
6.7	Data Integrity in Integrated eClinical Platforms: Dataflow and End-To-End Validation	96
6.8	Data Integrity for Electronic Documents Used in Clinical Trials: Electronic Signatures and Digital Signatures.....	97
6.9	Data Integrity for Electronic Documents Used in Clinical Trials: Certified Copy of Original Documents (Source Documents).....	98
6.10	Risk Identification for Data Integrity and Data Quality	100

7	Interfaces and Dataflows through Different Systems (eClinical Platforms/Architectures)	103
7.1	Generic eClinical Platforms versus Trial-Specific eClinical Platforms.....	105
7.2	Interfaces	106
7.3	Dataflow and End-To-End Validation	109
7.4	Validation in Different Organizations	111
8	Appendix 1 – References	113
9	Appendix 2 – Glossary	119
9.1	Acronyms and Abbreviations	119
9.2	Definitions	121

1 Introduction

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

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

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

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

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

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

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

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

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

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

1.1 Purpose

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

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

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

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