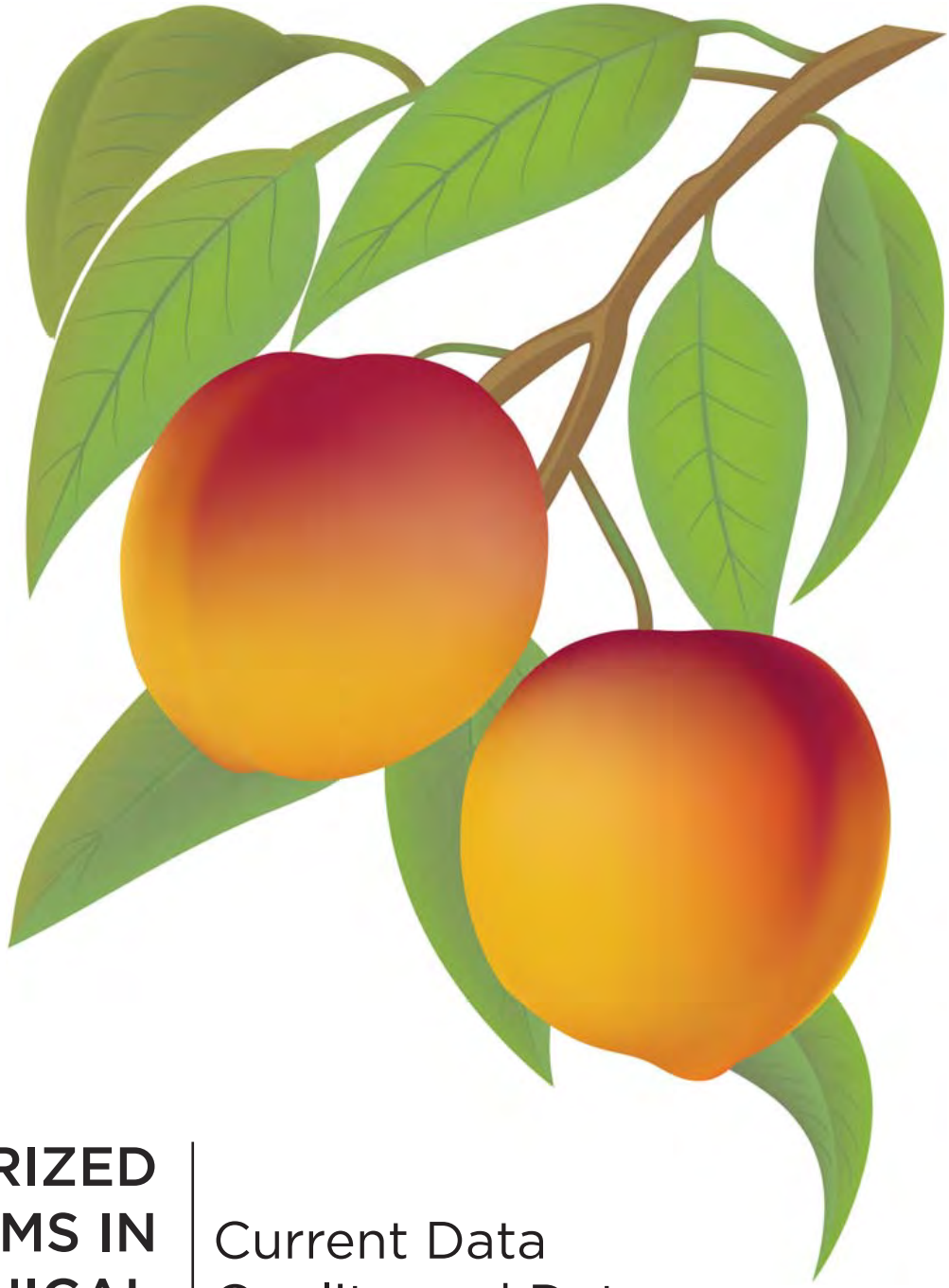

COMPUTERIZED SYSTEMS IN CLINICAL RESEARCH

Current Data Quality and Data Integrity Concepts

A continuation of the Red Apple effort in the clinical arena and designated as "Peach"

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Stéphanie Sallmann
Agence Française de Sécurité Sanitaire des Produits de Santé (French Health Products Safety Agency), France

Kevin Saylor
Millennium Pharmaceuticals, United States

Dr. Peter Schüler
ICON Clinical Research Plc, Germany

Hoi-Yan (Shum) Senecal
Hoffmann-La Roche, Inc., United States

Dave Smith
Roche Products Ltd., United Kingdom

J. Loren Smith
Genentech, Inc., United States

Barbara R. Snyder
Procter & Gamble Co., United States

Charlene Soyke
Procter & Gamble Co., United States

Dinamarie Stefani
Allergan, Inc., United States

Victor M. Stevens
Quintiles, United States

Matt Tedder
PharmaSys, Inc., United States

Dr. Heather Thomas
Watson Laboratories, Inc., United States

Jane Tucker
GlaxoSmithKline, United Kingdom

Shawn Wang
MedXview, Inc., United States

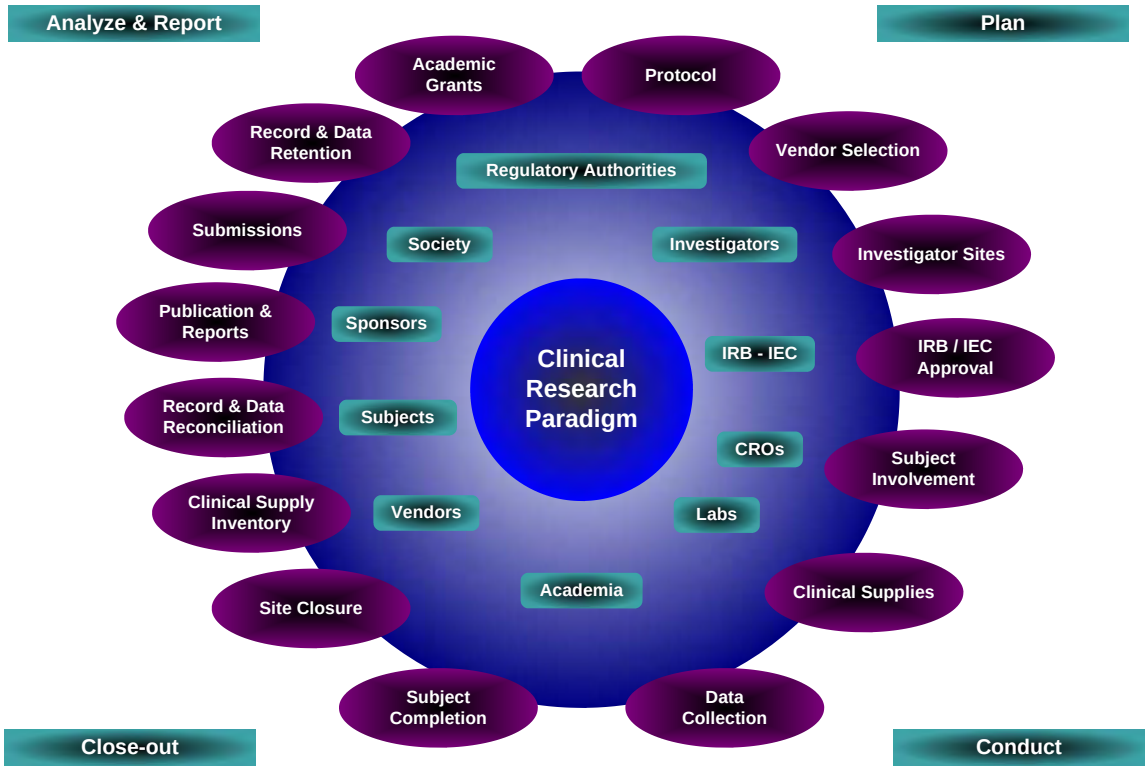
Phyllis Weldon
Eolus® Compliance Solutions, United States

J. Steven Wilkinson
MacroGenics, Inc., United States

Liz Wool
QD-Quality and Training Solutions, Inc., United States

INTRODUCTION

The clinical research paradigm presented here is the foundation selected to show the many stages, processes and stakeholders involved in clinical research. It is familiar and it is a life cycle. It is a guide to all simple and complex clinical research. Without this paradigm and its inherent processes, clinical research would be lost. These components are addressed in both layman and technical terms. The paradigm can teach the target audience of the advantages to successfully plan, test, secure, deploy, train and maintain computerized systems. This can be accomplished through the establishment of basic principles of this paradigm. This book is the benchmark for the design, verification, implementation and retirement principles of computerized systems used in clinical research. This approach allows the incorporation of tested concepts into best practices. These principles must be learned and, in some cases, the organization's behavior will have to be remolded and changed.



Definitions and References

This book contains a detailed Glossary that outlines specific terms and definitions. The reader is encouraged to review this Glossary during their use of this book. These terms and definitions were obtained from government documents, professional organizations and open literature. In addition, specific terms and definitions were created during the research and compilation of this book. In some cases, the definition or use of a term was modified for clarification.

There are many references within in the book to ICH, FDA guidances, EMA reflection papers and other regulatory references.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States, along with experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. This will help reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

The objective of such harmonisation is a more economical use of human, animal and material resources. It is crucial to eliminate the unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

This book is intended to reach out to all regulatory authorities and industry personnel, as such people need to take those local expectations into account as they read and absorb this information.

Best Practice

This initiative took into account all aspects of computerized systems in clinical research. The outcome as described in this book is a coherent set of current best practices.

Good Clinical Practice (GCP) really is a compilation of best practices and quality standards applied to the overall process of a clinical research. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, "Guideline for Good Clinical Practice (E6)," 1996, (ICH GCP), guidelines for "designing, conducting, recording and reporting" (and archiving) addresses the people involved and qualifies the standards by way of their responsibilities. Only one section of the E6 ICH Guideline (§5.5.3) addresses electronic systems. In addition, the GCPs have been interpreted and implemented differently by regulatory authorities (in the US Code of Federal Regulations, EU Clinical Trial Directives and Japanese regulations, for instance). Every region has additional guidance for the use of electronic systems (e.g., the US FDA 21 CFR Part 11, Eudralex volume 4, chapter 11) and data privacy and data protection (e.g., US HIPAA and Safe Harbor, EU 95/46, and Japan's PIPA).

Guidance on best practices for computerized systems often describe the practices from one particular view point (e.g., computer system hardware or software vantage). This book assesses the practices from the point of view of the overall clinical research process, thereby integrating the individual perspectives. Clinical research as defined by this effort includes academic, devices, and traditional and biologic drug development. The best practices and points to consider in this book have been thoroughly evaluated, researched and compared to existing methodologies, which will provide the reader with time-tested processes that will withstand the changes in technologies that constantly are occurring.

Basic Principles

This book is a benchmark for design, testing, implementation and retirement of computerized systems used in clinical research. It incorporates options that can be available for future applications and utilizing best practices. This approach to the successful utilization of computerized systems should enable the users to understand the principles outlined in this book. It is important to build quality and integrity into the processes from the beginning. These attributes cannot be added to the processes at a later date.

The contribution of all participants in this initiative (regulators, pharma, biopharma, academia, medicine and subject matter experts from all corners of the globe) guarantees that the basic principles and best computer system practices are current. This approach takes into account new ideas and technologies that the reader may apply.

Scope

Since the 1980s, there has been greater interest in electronic records in clinical research. This has forced the industry to apply innovation in assuring data quality and integrity.

Computerized systems have changed how clinical research is planned, conducted and reported. Government regulatory authorities worldwide are still reminding the industry to focus on subject safety, data quality and data integrity. Computers have "invaded" all aspects of life and clinical research is no different. This book is designed to help readers improve their clinical research computerized systems.

This book outlines the basic principles of computerized system design, testing and implementation, regardless of the type of computers or equipment being used in clinical research.

Data Quality and Data Integrity

Data quality has been defined by the *American National Dictionary for Information Systems, 1991*, as the "correctness, timeliness, accuracy and completeness that make data appropriate for use." According to sources at NIH who have adapted Dr. Joseph Juran's teachings on data quality, "data are of high quality if they are fit for their intended uses by customers in operations, decision making and in planning."

Integrity is defined by Roget Houghton Mifflin Company, Boston; *Roget's II: The New Thesaurus 3rd Edition*; 1995; page 552 as:

"Moral or ethical strength

The quality of being honest

The condition of being free from defects or flaws

The state of being whole"

It is easy to see how this definition can be applied to data. The data should be complete and accurate – without errors and a true and accurate representation of the situation (in the case of clinical research, the subject).

Data quality and data integrity have an impact on subject safety and the usability of the clinical information. Regulatory authorities have identified parameters that contribute to data quality. These have been "popularized" into the acronym ALCOA. To indicate the continuing identification of parameters this book utilizes the acronym ALCOA+.

Attributable – information is captured that identifies from where the data came e.g., lab equipment, a person, etc. *(**examples: audit trails and e-signature**)*

Legible – data are readable and understandable by humans. ***(examples: reports, tables and listings)***

Contemporaneous – data are recorded at the time they are generated or observed. ***(examples: time stamps & time-limited entry)***

Original – data are recorded for the first time. ***(examples: source data)***

Accurate – data are correct. ***(examples: calculations, algorithms and analyses)***

The ALCOA+ principles include the five attributes discussed above, plus additional parameters.

Enduring*:* data are preserved for its required lifetime and retrievable ***(examples: CD, magnetic tape, flashdrive or hard drive)***

Complete: All data are present ***(examples: all test results for subjects are kept, including metadata)***

Consistent: data are compatible, free from variation and non-contradictory ***(examples: use of standards)***

These are a slight expansion of the definitions of data quality and data integrity above. Clearly, it is important that someone has been assigned responsibility for the data and this responsibility is defined and documented. So, if questions or concerns arise, someone may respond to them.

So how can this be better described? Ensuring data integrity is rather like collecting artifacts at an archeological site. Trained individuals follow established procedures to ensure the details surrounding the identification, collection and storage of the artifact are documented. A chain of custody is followed to ensure the artifact is not contaminated or modified and that when the archeological find goes public, integrity of the artifact will be indisputable. If the chain is broken, reasonable doubt may be raised. The same holds true for data from a clinical trial no matter what instruments are used to gather the data.

Validation of Computerized Systems

Computer Systems Validation (CSV) is a process by which there is documented evidence that a product or process meets predetermined specifications and quality attributes. This book identifies the principles involved in successfully validating a system used in clinical research.

PREFACE

Why this Book is being Constructed?

In 1987, the US Food and Drug Administration planned, initiated and held a workshop in a remote resort (Red Apple Conference Center) in Arkansas. Industry and academia were invited to participate in this to establish a book on computerized systems used in non-clinical research. This event was revisited in 2006 and named Red Apple II, which made it clear that a similar initiative was needed for the clinical research arena.

The result is this book: *Computerized Systems in Clinical Research: Current Data Quality and Data Integrity Concepts*, which applies and further develops the standards set through Red Apple II in the context of clinical research. A large group of participants from the global clinical research arena carefully and exhaustively evaluated and compared the current use of science and technology to define best practices in the design, validation, application and use of computerized systems in the clinical research environment.

Why Now?

Computerized systems and electronic data management have been embedded into clinical research at a rapid pace in all kinds of applications. Sometimes, this progress seems hardly noticed. Many of the users of these computerized systems in clinical research environments are aware of the importance for data quality and data integrity. However, the clinical research community often underestimates the impact the use of electronic applications, use of computerized systems and the transmission of subject data may bring to the quality and integrity of data and the impact it may have on subject safety.

This initiative is intended to set a benchmark regarding requirements for computerized systems used in clinical research. It is simultaneously intended to support the many users struggling to implement validation processes into clinical research, stimulating innovation in the clinical research environment. Proper validation and use of computerized systems will help ensure the safety of subjects and the credibility of the clinical research data.

How this Book is Constructed

As with the initial Red Apple effort, described earlier in the preface, the passionate DIA members formed a Program Committee to direct and coordinate this new clinical project. The committee met bi-weekly for many months for planning, sketching out the general clinical research process, and defining the various functions, areas and disciplines, as well as the roles and responsibilities involved to create an initial scope and chapter outline. This scope imprint formed the basis for determining the experienced contributors needed for this clinical endeavor.

Following the successful Red Apple II recruitment process, the Program Committee through the resources of DIA issued a worldwide call for applicants. Applicants submitted a Web-based application providing background information of knowledge and experience, stating which clinical area they preferred (three options by priority). The Program Committee reviewed all applicants and their submitted

qualifications and interviewed many at the end of 2007 as potential chapter chairs for the envisioned chapters. Once chairs were identified and chosen, the committee then worked through June 2008 to select the remaining contributors for this clinical undertaking. Participation was worldwide and included every aspect of clinical research.

ACKNOWLEDGMENT

An endeavor such as this, by its very nature, has many individuals for which an acknowledgment is due.

We thank Joanne Wallace for all of her hard work and dedication to this effort and the Drug Information Association (DIA) for their support throughout this project.

The Peach participants are acknowledged for the significant investment of their time, travel, knowledge and experience in writing this publication. We wish also to thank the companies that supported their employees' participation. The efforts of all participants during the initial efforts in September of 2008 must be recognized for what it was – considerable sharing of ideas, negotiation and compromise in order to produce the most meaningful and useful publication possible.

The substantial efforts of the Program Committee, Advisor, Reviewers and Editorial Board in reviewing, critiquing and editing the manuscript as it developed to this final version were critical to completion of this book.

We are indebted to all the participants for their commitment.

(l to r) Richard Siconolfi, Joanne Wallace, Patricia Beers Block, Earl Hulihan, Richard Chamberlain, Joanne Malia, Helena M. van den Dugen

Participants of the Computerized Systems in Clinical Research Project

PARTICIPANTS

Program Committee

Earl Hulihan Professor (Committee Chair)
Medidata Solutions Worldwide, United States

Patricia Beers Block
Food and Drug Administration, United States

Richard Chamberlain, Ph.D.
ECS Inc., United States

Dr. Helena M. van den Dungen,
Inspectorate of Healthcare
Regulatory Agency, The Netherlands

Joanne Malia
Purdue Pharma, L.P., United States

Richard Siconolfi
Procter & Gamble Co., United States

Joanne Wallace
DIA Liaison, United States

Vicki Viamonte*
Peach Technical Writer,
Consultant, United States

Advisor

Dr. Nelson Kopyt
Northeast Clinical Research, Inc.,
United States

Reviewers

Dr. Cao Cai*
State Food and Drug Administration, China

Andy Cochrane
Medicines and Healthcare Products
Regulatory Agency, United Kingdom

Dr. Paul Foster
Development and Strategic Consulting
Associates, United States

Dr. Barbara Gladson
University of Medicine and Dentistry
of New Jersey, United States

Byungja E. Marciante*
Food and Drug Administration,
United States

Ashwin Mundra, Ph.D.
Medidata Solutions Worldwide, United States

Bob Tollefsen
Food and Drug Administration,
United States

Charlie (Charles) Willmer
Purdue Pharma, L.P., United States

Qing-Shan ZHENG, Ph.D.
Shanghai University of Chinese Medicine,
China

Dr. David Collier
William Marbury Research Institute,
United Kingdom

Brian R. Dakin
Rhombus Consulting, Inc., United States

Edsel David
Daiichi Sankyo, Inc., United States

Yves Dène
Sogeti Belux NV/SA, Belgium

Bernd Doetzkies
Daiichi Sankyo, Inc., United States

Terri Emerson
Cetero Research, United States

Loren Ferro
Western Institutional Review Board®
(WIRB®), United States

Andrew K. (Drew) Finnie
McDougall Scientific Ltd., Canada

Joseph A. Franchetti
JAF Consulting, United States

Kevin Gravesande
SUNY Downstate Medical Center,
United States

Nick Hargaden
Icon Clinical Research, United States

Dr. Peter Holthe
Roche Molecular Diagnostics, United States

James Huang
Almac Clinical Technologies, United States

Isara Isarowong
Allergan, Inc., United States

Michael Joos
AstraZeneca Pharmaceuticals LP,
United States

Phil Kirsch
SCHARP – Statistical Center for HIV/AIDS
Research & Prevention, Fred Hutchinson
Cancer Research Center, United States

Stephan Klaschka
Boehringer Ingelheim
Pharmaceuticals, Inc., United States

Mary B. Kuklinski
Bristol-Myers Squibb Company,
United States

Yeonkyung Lee
Janssen Korea Ltd., South Korea

Lisa Lewis
Novartis Pharmaceuticals Corporation,
United States

Daniel Liu, Ph.D.
Medidata Solutions Worldwide, United States

Rick Marcum
Quintiles, United States

Gladys Masi
Ethicon Inc., United States

Hitoshi Matsui
CAC Corporation, Japan

Monica Mattson
Celgene Corporation, United States

Dr. Sue Mayes
AstraZeneca, United Kingdom

Cheryl McCarthy
eClinical Solutions, a division of
Eliassen Group, United States

Walter (Neil) McClenney
VeriScientia, Inc., United States

John Nevy
The Children's Hospital of Philadelphia,
United States

Michael J. O'Grady
Invivodata, United States

Lisa Olson
i3, United States

Nancy Pasquan
Eyes On, Inc., United States

I. Alex Pawluk
Cephalon, Inc., United States

John Pentecost
Pentecost Consulting Services, LLC,
United States

Kenneth Rothfeld
Johnson & Johnson, United States