

# Implementing CDISC Using SAS<sup>®</sup>

An End-to-End Guide



Chris Holland and Jack Shostak

# Implementing CDISC Using SAS® An End-to-End Guide

Chris Holland and Jack Shostak



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## **Dedication**

Jack would like to dedicate this book to Linda, Chloe, and Alex for their continued patience with his writing hobby, his good friends in the CDISC community, and the fine folks at the Duke Clinical Research Institute that humor him on a daily basis. Thanks everyone.

Chris would like to dedicate this book to his wife and children: Kelly, Liam, Charlotte, and Luke for the joy they bring and smiles they invoke by simply being who they are. He would also like to acknowledge all of the dedicated CDISC volunteers who continue to work hard to develop and improve clinical trial data standards.



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# About This Book

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## Background

The Clinical Data Interchange Standards Consortium (CDISC) started in 1997 as a global, open, multidisciplinary, non-profit organization focused on establishing standards to support the acquisition, exchange, submission and archival of clinical research data and metadata. The mission of CDISC is “to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare.”

CDISC standards are promoted as being “vendor-neutral, platform-independent and freely available via the CDISC website.” When one speaks of clinical research data, however, one particular vendor often comes to mind. SAS software has been used for analyzing, summarizing, and reporting clinical trial data since the early 1980s. The US Food and Drug Administration (FDA) has required that electronic data provided to them in marketing approval submissions be formatted in the SAS version 5.0 transport file format. Although this format is now an open standard accepted by many types of software, it has played a role in establishing and maintaining SAS as the industry standard in the pharmaceutical industry for numerous tasks relating to clinical trial data.

The flagship standard developed by a CDISC working group is the Study Data Tabulation Model (SDTM). The term “tabulation” has its origins in the code of federal regulations (CFR) regarding what is required in New Drug Applications (NDAs). Specifically, 21 CFR 314.50 describes case report tabulations (CRTs) as “data on each patient in each study” that are “pertinent to a review of the drug's safety or effectiveness.” Originally, these tabulations were generated as listings on paper. However, by the late 1990s, electronic data sets were playing an increasing role in new drug reviews. As a result, the SDTM was developed as a standard data format for the electronic submission of these required tabulations.

Since the inception of CDISC, its bond with SAS and SAS users in the pharmaceutical industry has been a natural marriage. Over the past decade, as CDISC standards have built up momentum in terms of stabilizing and gaining regulatory approval and preference, SAS programmers have played an increasing role in the complete life-cycle of clinical trial data-- from collection, to analyzing, reporting, documenting, validating, submitting, and archiving data, and all the steps in between. As such, the time seems right to provide an end-to-end handbook for SAS users in the pharmaceutical industry who are working with CDISC standards.

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## Is This Book for You?

Any manager or user of clinical trial data in this day and age is likely to benefit from knowing how to either put data into a CDISC standard or analyzing and finding data once it is in a CDISC

format. If you are one such person-- a data manager, clinical and/or statistical programmer, biostatistician, or even a clinician, then this book is for you.

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## **Prerequisites**

It is assumed that the readers of this book have some basic understanding of SAS programming. It is also advantageous if the reader has some familiarity with the CDISC SDTM and ADaM models. If you do not have this knowledge then there will be some portions of this book that will be more difficult to follow.

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## **Purpose**

This book has two purposes. One is to introduce readers to the end-to-end process for implementing CDISC standards on clinical trial data. The second is to introduce readers to SAS-based tools that can not only facilitate the implementation process but also facilitate the ultimate goal of analyzing your data once it follows a CDISC standard. Some of these tools are actual SAS products. Some are SAS macros provided by the authors.

In order to achieve these goals, the authors have created fictional clinical trial data that will be used to provide examples of how to apply SAS tools to the various steps in the process along the way.

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## **Organization and Scope of This Book**

With the end-to-end concept in mind, this book is organized with a start-to-finish mentality for clinical trial data. Chapter 1 starts with an overview of the primary standards covered in this book, the SDTM and the Analysis Data Model (ADaM), and a discussion of considerations as to when each should be implemented. Chapter 2 is focused on what should be the first step to any big project, the specifications. Although many currently think of the creation of metadata and data documentation as part of the process that comes after building the datasets, the authors hope that the tools and tips provided here will facilitate the creation of a `define.xml` as a tool for implementing SDTM standards before any of the actual conversion work is performed.

Chapters 3, 4, and 5 all cover SDTM implementation, but with different tools (Base SAS, SAS Clinical Standards Toolkit, and SAS Clinical Data Integration, respectively). Chapters 6 and 7 relate to ADaM metadata and implementation, respectively. With regulatory, quality, and compliance concerns in mind, Chapters 8 and 9 cover SDTM and ADaM validation. Chapter 10 is about analyzing data that have been structured to follow CDISC standards, with a particular focus on JMP Clinical, which has been specifically developed to work on SDTM and ADaM data. Finally, concluding the “end-to-end” process, Chapter 11 provides information on how to integrate your data from various studies into one integrated database and other steps required for providing your data in a regulatory submission.

Although many CDISC standards have stabilized, there are new standards on the horizon. Chapter 12 looks at some of these uncertainties, such as the Janus clinical trial data repository and HL7 messaging for CDISC content. Other topics relating to CDISC standards are covered here as well,

such as the SEND model for non-clinical data and the BRIDG model for relating HL7, CDISC, and other standards, models, and semantics together.

What is not covered in this book are details, guidelines, and examples on how to put certain types of data into the CDISC models. These are details that CDISC therapeutic area working teams are most adept at dealing with. The SDTM implementation guide (IG), contains a wealth of knowledge pertaining to how, when, and where to put clinical trial data in SDTM domains. Similarly, the ADaM IG and associated appendixes have more information to help implementers decide how to build ADaM datasets.

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## **Software Used to Develop This Book's Content**

As you might expect, the majority of the software used in this book is SAS software. The following software was used in the production of this book:

- Base SAS 9.3
- SAS Clinical Standards Toolkit 1.3
- SAS Clinical Data Integration 2.1
- JMP 9
- JMP Clinical 3.1
- Open CDISC Validator version 1.2.1

Various versions of Internet Explorer and Chrome were used to render the define.xml files

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## **Data and Programs Used in This Book**

The majority of the source data for this book can be generated by the SAS programs found in Appendix A of this book. There is some study metadata used to generate the Trial Design Model datasets for the SDTM that you can find in Microsoft Excel files on the author pages listed below. The metadata spreadsheets used for the ADaM and SDTM data can also be found at the author pages listed below. Finally, all programs used in this book can be found on the author pages as well.

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## **Author Pages**

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- <http://support.sas.com/shostak>

The author pages include all of the SAS Press books that these authors have written. The links below the cover image will take you to a free chapter, example code and data, reviews, updates, and more.

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## Example Code and Data

You can access the example code and data for this book from the author pages listed in the previous “Author Pages” section. Once on the author page select “Example Code and Data” to display the SAS programs that are included in this book.

For an alphabetical listing of all books for which example code and data is available, see <http://support.sas.com/bookcode>. Select a title to display the book’s example code.

If you are unable to access the code through the Web site, send e-mail to [saspress@sas.com](mailto:saspress@sas.com).

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## Additional Resources

SAS offers you a rich variety of resources to help build your SAS skills and explore and apply the full power of SAS software. Whether you are in a professional or academic setting, we have learning products that can help you maximize your investment in SAS.

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## About The Authors



Chris Holland has been a SAS user since 1990. He currently works as a Biostatistics Director for Amgen and has prior experience heading up biostatistics departments for Sunovion Pharmaceuticals, MacroGenics, and Mercknet. He has also worked as a statistical reviewer at the Center for Drug Evaluation and Research in the U.S. Food and Drug Administration. There he served as the technical lead for the SDTM/ADaM Pilot Project review team, which included FDA staff involved with assessing the suitability of CDISC standards for meeting the needs of

medical and statistical reviewers. Holland continues to be active in the CDISC community, particularly with the ADaM team. He received an MS in Statistics from the University of Virginia, and a BS in Statistics from Virginia Polytechnic Institute and State University. He is an Accredited Professional Statistician™ by the American Statistical Association.



Jack Shostak, Associate Director of Statistical Programs at the Duke Clinical Research Institute. A SAS user since 1985, he is the author of *SAS Programming in the Pharmaceutical Industry*, and co-author of *Common Statistical Methods for Clinical Research with SAS Examples, Third Edition*, both published by SAS Press. Shostak has published papers for the Pharmaceutical SAS Users Group (PharmASUG) and the NorthEast SAS Users Group (NESUG), and he contributed a chapter, "Reporting and SAS Level Selection," in the book *Reporting from the Field*. Jack is active in the CDISC community, contributing to the development of ADaM and the Statistical Domain Analysis Model, and he serves as a CDISC ADaM trainer. He received an MBA from James Madison University, and a BS in Statistics from Virginia Polytechnic Institute and State University.

Learn more about these authors by visiting their author pages, where you can download free chapters, access example code and data, read the latest reviews, get updates, and more:

- <http://support.sas.com/holand>
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# Acknowledgments

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# Chapter 1: Implementation Strategies

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## Why “CDISC It”?

The decision to adapt to CDISC standards within an organization or for a particular clinical development program is not an easy one. Many large pharmaceutical companies have their own internal standards and tools built around those standards. For these companies, the decision about if and when to switch to CDISC was, and in many cases still is, fodder for heated debates. Upper management may cringe and balk at proposals to implement CDISC standards when they see the up-front price tag associated with it. Some organizations got burned by trying to implement the Study Data Tabulation Model (SDTM) too early, before FDA reviewers were prepared for it and before the standard had stabilized to a point where it was backwards compatible. Without an FDA mandate, the rationale for taking a wait-and-see approach seemed to have its merits.

Despite these concerns, set-backs, and growing pains for CDISC, the groundswell of support continued to rise. Mergers and acquisitions have persisted throughout the pharmaceutical industry, and behind the scenes of each merger are the data managers and SAS programmers who’ve worked at the same desk year after year, but have seen their employer name change three to four times. Throughout it all, with a change in the employer came the change in the case report form (CRF) designs, variable names, and data formats for the different compounds on which they worked. When it came time to integrate the data for a regulatory submission, a substantial amount of time was spent deciding on the structure and variable names to be used for the integrated database. And that was just the beginning. The time spent doing the actual conversions and integration is often much greater. As the programming hours piled up, those involved started to see the merits of having a standard across the industry.

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## 2 Implementing CDISC Using SAS: An End-to-End Guide

Pharmaceutical and biotech companies weren't the only organizations undergoing mergers. During the late 1990s and early 2000s, many CROs consolidated as well. In addition to the numerous data standards they had to keep track of among their various clients, CRO SAS programmers also had to deal with different data formats being used internally due to consolidation with other CROs. Some at these CROs got to work on integration projects involving compounds that, at each new phase of development, had been passed from one organization and CRO to another. As a result, even the most basic key identifier of any clinical trial dataset, the subject ID, was sometimes uniquely named within each study. So as the programming hours piled up, the key decision makers at CROs started to see the merits of having a data standard across the industry.

Yet this grass-roots initiative to develop industry-wide standards would not have gotten off the ground without the support of the biggest consumer of clinical trial data of all, the US Food and Drug Administration. Although some FDA reviewers become accustomed to data formats they see from certain sponsors, most still have to deal with completely different data formats and structures from one sponsor to the next. This might not have been so cumbersome in the days before the Prescription Drug User Fee Act (PDUFA, commonly pronounced *puh-DOO-fa*) first became effective. Before PDUFA, a review clock was non-existent and 2-year reviews of New Drug Applications (NDAs) and Biologic License Applications (BLAs) were the norm. However, with the passage of PDUFA, review cycles were originally mandated to be 12 months (and are now down to 10 months). With those review clocks, along with increasing expectations to carefully inspect the electronic data that were packaged with NDA and BLA submissions, reviewers found themselves having to do more with less.

The aftermath of some pivotal events in 2004 put even more pressure on FDA reviewers. One was the investigation of suicidality risks among children on antidepressants. The other was the withdrawal of Vioxx from the market. Because of these two high-profile safety concerns, doctors, patients, and sponsors all suddenly had a vested interest in knowing whether the drugs they were prescribing, taking, or selling to treat depression, arthritis, or any number of spin-off indications were adding on risks that outweighed the benefits. The brunt of these class-effect determinations fell on the FDA clinical and statistical reviewers who were the only ones who had access to all the data that would allow them to make the informed decisions that the public, doctors, industry, congressmen, and media were all suddenly demanding. However, when the drug class under consideration involved 10 different compounds from as many different sponsors with as many different data formats, this was no easy task. "Wouldn't it be great," some FDA reviewers asked, "if we had all the data we need in one giant database?" Fortunately, within the FDA, certain reviewers, team leaders, and division directors all started to see the merits of having a data standard across the industry. To coin a common phrase of one particular FDA division director who had a penchant for promoting data standards at industry conferences, the mantra of the late 2000s became "just CDISC-It."

Evidence of FDA's support of data standards is not only found at conference podiums. Since the draft release of version 3.1 of the SDTM Implementation Guide (IG) in October, 2003, the FDA has issued a number of documents indicating their support of data standards. A summary of these appear in Table 1.1.

**Table 1.1: FDA Documents and Events in Support of Data Standards**

<b>Time</b>	<b>Event</b>
July, 2004	eCTD study data specifications reference the SDTM for tabulation data
March, 2006	“Development of data standards” listed as opportunity #44 in the FDA’s Critical Path opportunities list
September, 2006	SDTM/ADaM pilot project review completed and results presented at the CDISC Interchange
September, 2006	Old e-NDA guidance document is withdrawn (leaving the eCTD study data specifications as the only guidance relating to submission data)
December, 2006	Proposed rule to require electronic data with submissions is released in the Federal Register
May, 2008	First version of the PDUFA IV IT plan is released, making numerous commitments to the SDTM
October, 2009	Version 1.5 of the study data specifications released, making specific reference to the Analysis Data Model (ADaM) standard for analysis data
March, 2010	Version 1.0 of the CDER Data Standards Plan released, providing a commitment to CDISC standards
May, 2011	The “CDER Common Data Standards Issues Document,” version 1.0 is released, stating that CDER is “strongly encouraging sponsors to submit data in standard form”
February, 2012	Draft FDA guidance document <i>Providing Regulatory Submissions in Electronic Format -- Standardized Study Data</i> (a.k.a. “the e-Data Guidance”) released to establish “FDA’s recommendation that sponsors and applicants submit study data in a standardized electronic format”

Nowadays, the legion of CDISC implementers is tangible to any attendee of a SAS user conference struggling to find an empty chair in a session that has anything to do with CDISC. Managers are preaching the data standards gospel, software vendors are demonstrating their tools that make use of CDISC data, FDA presenters are promoting their preference for CDISC, and FDA documents are recommending the SDTM and ADaM models as the format to use for sponsors’ NDA and BLA submissions.

Despite all this, electronic data submissions are still (believe it or not) optional. Many compounds struggle to get beyond Phase I of development. Implementers have struggled with different interpretations of the standards and with study-specific data that don’t seem to have a clear-cut home in the SDTM IG. So while the decision to “CDISC-It” for a regulatory submission has become more clear-cut, the stage when the CDISC conversion takes place, and how far to go with it, is less lucid. Study phase, organizational size, standards know-how, and the amount of resources all factor in to the decision-making equation.

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