

Considerations in Submitting Standardized Electronic Data Under the Animal Rule: The Use of SDTMIG and SENDIG Domains, and the Need for New Domains and Concepts

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ABSTRACT

The Animal Rule (AR) in the Code of Federal Regulations (CFR) provides a mechanism for the approval of drugs (1) and biological products (2) without requiring human clinical trials for efficacy when to do so is not ethical or feasible. Instead, the AR allows efficacy studies to be conducted in animals, with certain requirements. Examples of products covered under the AR are vaccines against diseases such as smallpox and anthrax. Product safety testing in humans is still needed, but the requirements for this are out of scope for this paper.

In conjunction with the Critical Path Institute (C-Path), CDISC is currently engaged in an effort to develop an implementation guide for AR studies. The FDA's Counter-Terrorism and Emergency Coordination Staff (CTECS; within CDER) has provided their data requirements. These include the use of domains from the Standard for the Exchange of Nonclinical Data Implementation Guide (SENDIG) and the Study Data Tabulation Model Implementation Guide (SDTMIG), the development of new domains, and the creation of new Trial Summary parameters. It is also expected that new SDTM variables and concepts will be required. This paper will discuss initial considerations in developing such an implementation guide for AR studies and further describe the standards, both existing and new, needed to support submissions under the AR.

INTRODUCTION

The Animal Rule is found in the Code of Federal Regulations (CFR) (1, 2) and it provides a mechanism for the approval of drugs and biological products without human clinical trials for efficacy. It allows efficacy studies to be conducted solely in animals in cases where studies in humans are not ethical or feasible. Human clinical trials are still required to evaluate the safety of the product, and for determining the appropriate human dose(s). The AR applies only to products developed to ameliorate or prevent serious or life-threatening conditions caused by chemical, biological, radiological, or nuclear substances. CDER and CBER have jointly issued a guidance document on conducting AR studies (3). Since this document is relatively new (2015), it implements the electronic submission requirements of Section 745A(a) of the FD&C Act (4). This guidance mentions that additional guidances will be published for more specific areas. One of these (5) requires standardized electronic study data. This means that once data standards have been developed for AR studies, their use will be required in future regulatory submissions.

In order for product approval to be granted under the AR, 1) the safety of the product in humans must have been demonstrated, and 2) "adequate and well-controlled the animal studies" must have established that the product is reasonably likely to produce a clinical benefit in humans. There are four criteria, all of which must be met in order for FDA to rely on animal data for efficacy (1, 2, 3). These are as follows:

- *"There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product.*
- *The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.*
- *The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity.*

- *The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.”*

The FDA Guidance (3) provides a considerable amount of detail regarding the essential elements of an animal model, as well as design considerations for adequate and well-controlled studies in animals.

The FDA’s Counter-Terrorism and Emergency Coordination Staff (CTECS; within CDER) had performed some preliminary assessment of existing CDISC standards that could be used for applications supporting products developed under the Animal Rule. They determined that these standards were not entirely sufficient to facilitate reviews of the data they needed and expected. As a result, an RFP was issued (6). The request was for an organization(s) to develop and publish CDISC standards for AR studies 1) using an open, consensus-based data standards-development process, and 2) incorporating any relevant standards from Standard for Exchange of Nonclinical Data (SEND) and Study Data Tabulation Model (SDTM), and its implementation guide. This effort would also include the development of any new standards necessary to represent data from these studies.

CDISC, in collaboration with the Critical Path Institute, applied for and was awarded the RFP. The ultimate goal is to develop an implementation guide for AR studies based upon the SENDIG. The FDA (CTECS) has provided their recommendations for domains and concepts needed to support the submission of these studies. They include a combination of domains from the SDTMIG and the SENDIG in addition to some new domains and concepts. An evaluation of how the data will be represented has recently begun by a CDISC/C-Path project team, and is currently underway. The layout and exact content of an implementation guide for AR studies (most likely referred to as the SENDIG-AR) is under discussion.

Since the standards-development effort for AR studies has just recently begun at the time of this writing, the following sections of this paper describe what the authors consider to be the likely needs for data standards to support these studies. These include the following:

- Domains within the SDTMIG that would be applied to animal studies, with new assumptions and examples
- Domains within the SENDIG that would need additional assumptions and examples
- New domains not currently in the SDTMIG or the SENDIG
- New SDTM variables for new concepts
- New parameters for Trial Summary

All development will follow the CDISC Standards Development Process (CDISC-COP-001).

Definitions used in this paper include the following:

- A *challenge agent* is the substance used to cause the disease or condition in animal studies. In human studies, this is referred to as an etiological agent.
- A *medical countermeasure (MCM)* is a material designed to treat the disease or condition. In AR studies, it is the study treatment.

Acronyms used in this paper are described in their first appearance, but can also be found at the end of this paper.

TYPES OF STUDIES NEEDING TO BE COVERED

CTECS has identified four major types of studies for which the standards created by this project will apply. These study types are described in the paragraphs below, and in the concept map that follows.

NATURAL HISTORY STUDIES

Natural history studies define the animal model in which efficacy will be tested. In these studies, animals are exposed to a challenge agent and monitored to gain an understanding onset, progression, and

manifestations, as well as any biomarkers of the disease or condition. It's important to understand the similarities and differences between humans and the animal model. The FDA Guidance (3) provides expectations for the design of such studies.

TREATMENT STUDIES

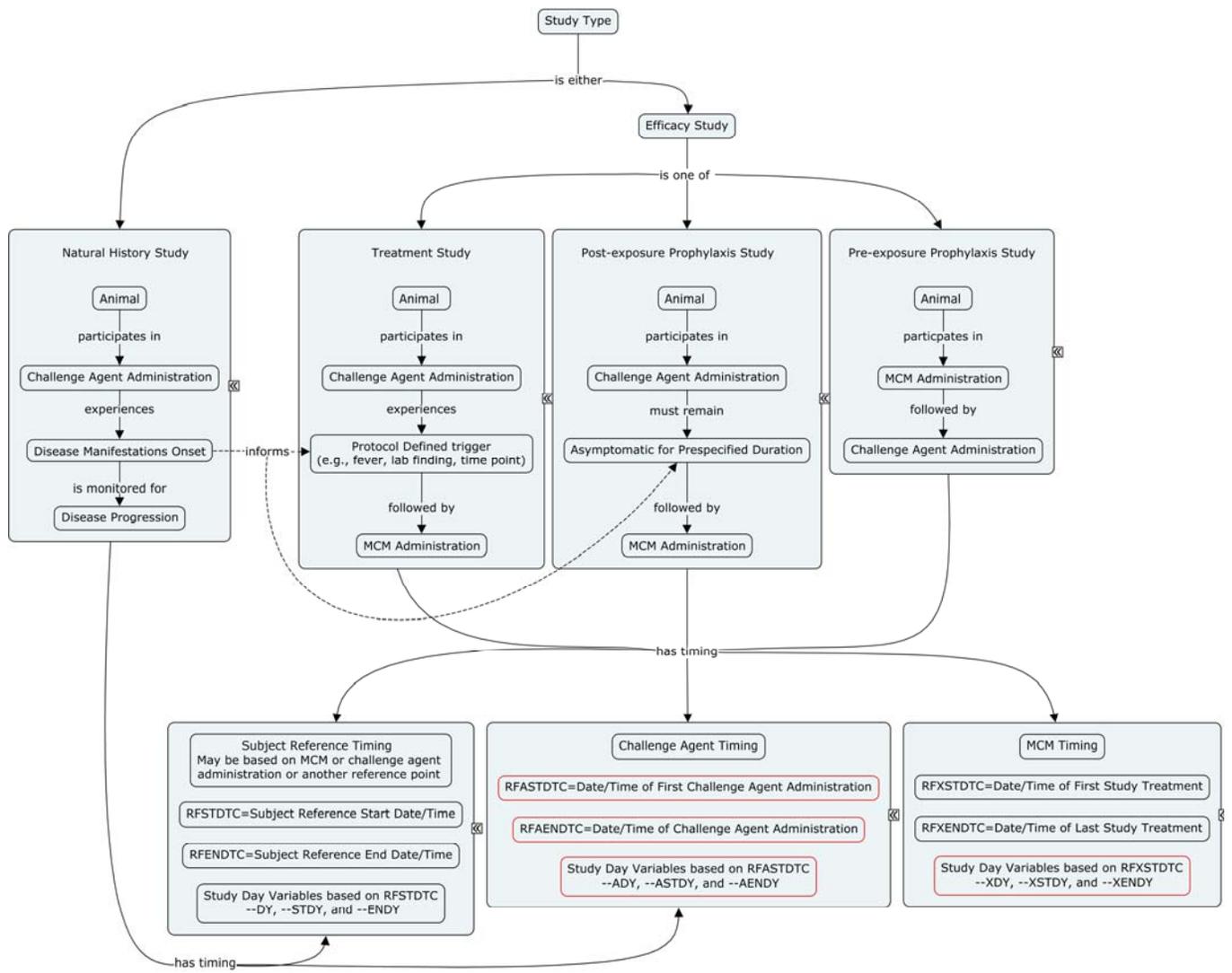
In Treatment Studies, animals are exposed to the challenge agent, and then treated with the medical countermeasure (MCM) when pre-defined signs and symptoms that were identified in the Natural History Study appear.

POST-EXPOSURE PROPHYLACTIC STUDY

Post-Exposure Prophylactic Studies are similar to the Treatment Studies, except that treatment with the MCM occurs after exposure to the challenge agent, but prior to the development of any signs or symptoms. The estimated elapsed time between exposure to the challenge agent and the development of signs or symptoms is determined during the Natural History Study.

PRE-EXPOSURE PROPHYLACTIC STUDY

In Pre-Exposure Prophylactic, animals are given the MCM prior to being exposed to the challenge agent.



SENDIG DOMAINS EXPECTED TO BE USED

It is expected that almost all of the domains in the SENDIG, as shown in the table below, would be used as needed, and require either no or very few changes. Additional examples, controlled terminology, and assumptions will likely be needed, however.

Special Purpose

- Demographics (DM)
- Comments (CO)
- Subject Elements (SE)

Interventions

- Exposure (EX)

Events

- Disposition (DS)

Trial Design

- Trial Elements (TE)
- Trial Sets (TX)
- Trial Arms (TA)
- Trial Summary (TS)

Findings

- Body Weight Gains (BG)
- Body Weights (BW)
- Clinical Observations (CL)
- Death Diagnosis (DD)
- ECG Test Results (EG)
- Food and Water Consumption (FW)
- Laboratory Test Results (LB)
- Macroscopic Findings (MA)
- Microscopic Findings (MI)
- Organ Measurements (OM)
- Palpable Masses (PM)
- Pharmacokinetics Concentrations (PC)
- Pharmacokinetics Parameters (PP)
- Subject Characteristics (SC)
- Vital Signs (VS)

Relationships

- Supplemental Qualifiers (SUPP--datasets)
- Related Records (RELREC)
- Pooling (POOLDEF)

SDTMIG DOMAINS EXPECTED TO BE USED

CTECS has indicated that the SDTMIG domains listed below may be needed for AR studies. The implementation of these domains in AR studies is not expected to be different than that for the implementation in human clinical trials, although animal-specific examples may be needed.

- Concomitant Medications (CM)
- Exposure as Collected (EC)
- Protocol Deviations (DV)
- Medical History (MH)
- Procedures (PR)

NEW DOMAINS EXPECTED TO BE CREATED

The following domains have not been modeled in either the SDTMIG or SENDIG. Domain codes have not been finalized.

- Challenge Agent Characterization
- Medical Countermeasure Characterization
- Challenge Agent Exposure

CTECS has expressed an interest in receiving data on the characterization of both the challenge agent and the MCM. Included are a number of physical and chemical properties that will likely be modeled in a parameter/value fashion similar to that used for Trial Summary.

Challenge Agent Exposure may be represented as a new Interventions domain. The Procedure Agents (AG) domain, which will be included in the SDTMIG v3.3 later this year has been suggested, but discussion has just begun.

PROPOSED ADDITIONAL TIMING VARIABLES

To put the need for new Timing variables into perspective, an overview of the existing variables is provided below.

EXISTING TIMING VARIABLES

The Demographics domain in the SDTM and both the SDTMIG and SENDIG provides a number of anchors (reference date/times) for use in a study. These include the following:

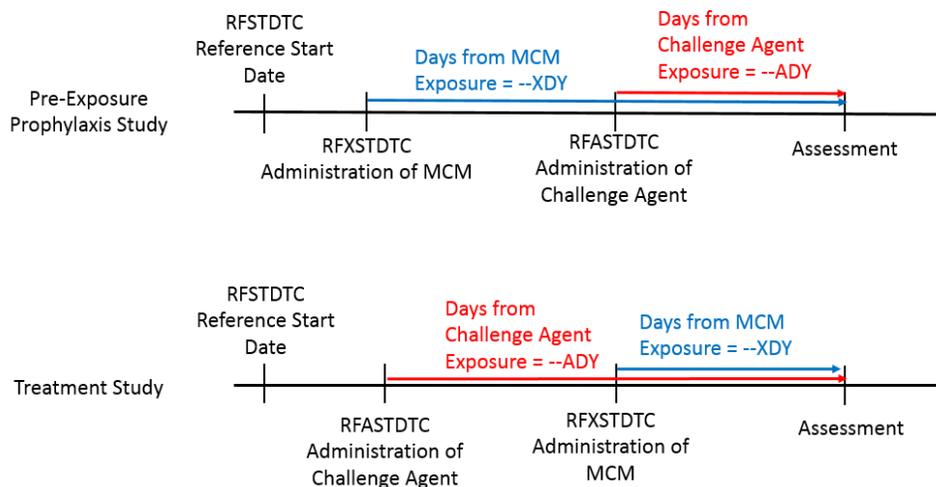
- RFSTDTC: The reference start date, which is Study Day 1, and is often, but not always, the first date of exposure to study treatment.
- RFENDTC: While this variable is expected in both the SDTMIG and SENDIG, it is rarely used as an anchor.
- RFXSTDTC: The first date/time of exposure to any protocol-specified treatment or therapy, equal to the earliest value of EXSTDTC.
- RFXENDTC: The last date/time of exposure to any protocol-specified treatment or therapy, equal to the latest value of EXENDTC (or the latest value of EXSTDTC if EXENDTC was not collected or is missing).
- The general-observation class-domains use the following Timing variables from the SDTM Table 2.2.5, which are based upon the RFSTDTC: --DY, --STDY, and --ENDY.

ADDITIONAL TIMING VARIABLES

Additional Timing variables are proposed as follows:

- Anchors in Demographics for the first and last dosing of the challenge agent. These have been tentatively designated RFASTDTC and RFAENDTC.
- Variables for use in the general observations classes for days since challenge agent administration. These are proposed to be --ADY, --ASTDY, and --AENDY. At this time, however, it's not known whether these will be based on the first or last dose of challenge agent, although variables for both may be required.
- Variables for use in the general observations classes for days since MCM (study treatment administration). These are proposed to be --XDY, --XSTDY, and --XENDY. These are needed because RFSTDTC can't always be guaranteed to be the first date of exposure.

How these would interact is shown for two types of studies in the figure below.



ADDITIONAL CONCEPTS THAT MAY BE NEEDED

Because a number of the etiological agents for which countermeasures are developed are intended to be inhaled by humans, simulating this route of exposure in animals is important. Understanding actual doses via this route is complicated by the fact that there are a number of ways to represent “exposure”. Air concentrations are one method, but more detailed determinations are often dependent upon taking into account respiration rates and minute volumes. These concepts have not yet been modeled in SDTM-based domains, and will likely be needed in studies with challenge agents whose primary route of exposure is via inhalation.

THE FUTURE

While preliminary work has begun by a small group representing CDISC and the Critical Path Institute, a larger team of interested members from the data-standards community will be formed. A number of SEND Team members have already volunteered. Critical in the development of an implementation guide will be obtaining data from real submissions that can be blinded and mapped to the domains modeled for this purpose.

As with other CDISC standards, NCI’s Enterprise Vocabulary Services will be involved in developing the necessary controlled terminology for any new domains, as well as for new parameters needed for existing domains.

As mentioned previously, the end deliverable for the RFP is an implementation guide based upon the SENDIG, likely to be called the SENDIG-AR. The final deliverable is planned for 2018.

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ACRONYMS USED IN THIS PAPER

AR	Animal Rule
CDER	Center for Drug Evaluation and Research (FDA)
C-Path	Critical Path Institute
CDISC	Clinical Data Interchange Standards Consortium
CTECS	Counter-Terrorism and Emergency Coordination Staff
FDA	Food and Drug Administration (U.S.)
IND	Investigational New Drug (Application)

MCM Medical Countermeasure (Study Treatment)
NDA New Drug Application
SDTM Study Data Tabulation Model
SDTMIG SDTM Implementation Guide: Human Clinical Trials
SEND Standard for Exchange of Nonclinical Data
SENDIG SEND Implementation Guide

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