



Recommendations for Populating Control Type (TCNTRL) with CDISC SEND Controlled Terminology

1. Overview: Purpose of this Document

The purpose of this white paper is to propose harmonisation for control type (TCNTRL) terms and definitions to improve historical background control analyses of SEND data. The TCNTRL parameter in the Trial Sets (TX) domain is used to define the control type for the control group. The control type is currently populated as free text, which results in ambiguity regarding designation of the type of control group (e.g. vehicle or negative control versus positive control). The lack of controlled terminology for the TCNTRL field decreases search result confidence and limits the number of records available for historical background control analyses.

In July of 2020, PHUSE announced the creation of a Working Group project entitled Harmonization of SEND Implementation to Enable Historical Control Data Analysis as a collaboration between BioCelerate and the PHUSE Computational Science Symposium's Nonclinical Topics Working Group to address SEND harmonisation issues.

This white paper recommends implementation of controlled terminology for the control type (TCNTRL) parameter in the TX domain for SENDIG 3.0 and SENDIG 3.1 datasets in order to increase search result confidence when determining background control findings. Use of controlled terminology will increase the accuracy and value of SEND data by providing standard terms and definitions to identify vehicle/negative control types for comparison and differentiate from the positive control (causing an anticipated change) animals. This type of data is used to determine whether toxicology findings are compound-related or background. The delineation of background control findings in animals is an important factor in the interpretation of toxicology study findings.

2. Scope

The controlled terminology recommendations for TCNTRL are intended to harmonise and define control types for parallel design toxicology studies. Other types of study design (e.g. crossover, dose escalation, factorial and Latin square) are out of scope since the designs generally do not include animals that only received vehicle/negative control material. Parallel study design is the most common type of toxicology study design; therefore, the ability to accurately search on control type will create larger datasets for defining background control findings.

3. Definitions

CT: Controlled Terminology
 TCNTRL: Control Type
 TX: Trial Sets
 CDER: Center for Drug Evaluation and Research
 CDISC: Clinical Data Interchange Standards Consortium
 FDA: Food and Drug Administration
 SEND: Standard for Exchange of Nonclinical Data
 SENDIG: Standard for Exchange of Nonclinical Data Implementation Guide

4. Problem Statement

Scientists often need to determine whether findings in toxicology studies are a result of compound treatment or normal background findings. When a scientist (e.g. a study director, pathologist) queries SEND data for background control findings, it is important to accurately categorise the different control groups (e.g. the positive control groups and the vehicle/negative control groups). SEND datasets include control group information in the TX domain using TCNTRL as free text, which leads to the use of ambiguous terms that do not clearly differentiate the various types of control groups. Therefore, generating searches to confidently identify vehicle/negative control animals is not possible. This white paper proposes controlled terminology for the TCNTRL variable to address the issue.

5. Background

In the manuscript [Leveraging the Value of CDISC SEND Datasets for Cross-Study Analysis: Incidence of Microscopic Findings for Control Animals](#), data from the FDA CDER SEND dataset repository was analysed to identify vehicle/negative control animals. The TCNTRL variable of the TX domain was populated over 90% of the time in >1,800 sponsor-submitted SEND datasets. A list of the terms entered in the TCNTRL field of the TX domain are provided in Section 8.1 (Examples of Control Type (TCNTRL) Descriptions Submitted to the FDA in SEND). The list shows that TCNTRL was entered as free text including the use of synonyms and ambiguous terms. Based on this data, it was determined that application of controlled terminology for this variable when these datasets were prepared would increase the effective size of the historical control dataset from approximately 71% to 98% of the records. Use of controlled terminology is expected to result in a 38% increase in the number of confidently identified records available for analysis, underscoring the importance of establishing controlled terminology for TCNTRL to distinguish vehicle/negative controls from positive controls.

At the PHUSE CSS 2020, the Nonclinical Topics Working Group evaluated the proposal of using controlled terminology for the control type (TCNTRL) variable. The Working Group concluded that the use of controlled terminology is a straightforward solution that does not require changes to the data structure. Participants also noted it would have exceptional value for historical control use cases, cross-study analyses or individual study analysis, and determined it to be a high priority.

6. Recommendations

6.1. Recommendations for Control Type (TCNTRL) Controlled Terminology

This white paper recommendation is to use controlled terminology for TCNTRL. This will increase the number of vehicle/negative control group records usable for analysis by approximately 38%. This increase in the number of properly classified records shows the importance of implementing controlled terminology for TCNTRL to distinguish vehicle/

negative control animals from positive control animals when evaluating background control findings. Currently, the CDISC Controlled Terminology team is developing a codelist for control type (CNTRL) that is in alignment with the suggestions in this white paper.

6.2. Recommendations for TCNTRL Controlled Terms

See below a list of the proposed TCNTRL controlled terminologies for CDISC to consider. Definitions were adapted from the draft work of the CDISC CT team.

Requested Submission Value for Control Type	Example(s)	Definition
Vehicle Control	Control Vehicle Vehicle Vehicle Control Vehicle Control Article PEG Control Reference Item Saline Control Water Water Control	The material used to prepare the test article/test item formulation for administration to animals or a test system. A vehicle control is administered to an animal or test system the same way as the formulated test article/test item. The purpose of the vehicle control is to determine the potential effects caused by the vehicle alone.
Negative Control	Negative Control Placebo Placebo Control Reference Item Saline Control Water Water Control	A chemical/compound administered to animals or a test system that is not expected to cause the anticipated change(s) caused by the formulated test article/test item. The purpose of the negative control is to ensure administration of a test article or vehicle is not adversely affecting the animals or the test system in the experiment, which might result in a false-positive conclusion.
Positive Control	Positive Control Positive Control Article	A chemical/compound administered to an animal or test system that is expected to cause an anticipated change(s). The purpose of the positive control is to provide a standard, within the study, to measure differences in the level of response among test groups. Positive controls are also used to demonstrate that a response can be detected.
Procedural Control	Sham Sham Control Vector Control	Typically used for studies involving surgical procedures. Used to account for the potential effects related to the procedure or treatment without the actual use of the test article/test item or therapeutic device. A sham control in a dermal study is used to account for any irritation caused by the applicator.
Untreated Control	Untreated No-treatment Control	The group of animals or replicates of a test system that are not treated or given any substance. In dietary studies, untreated laboratory animal diet is used for this group (sometimes referred to as "cage control"). The purpose of this group or replicate is to account for baseline responses under the conditions of the test system independent from the vehicle control or test article/test item.
Air Control	Air Air Control	Used mainly for inhaled route studies to account for the effects on the respiratory patterns, systems and behaviour that additional air, as well as dosing, procedures have on the animals since air acts as a carrier for dosing delivery. This air control acts as a standard against which the effects of the delivery of the test article/test item and vehicle control can be compared.

7. Conclusion

Industry is encouraged to adopt the proposed approach to populate TCNTRL using controlled terminology being developed by CDISC. The controlled terminology and definitions will increase the accuracy and value of SEND data to determine background control findings versus treatment effects. This will help in identification of historical control findings to enable identification of compound-related effects and also improve individual study or cross-study analysis.

8. Appendix

8.1. Examples of Control Type (TCNTRL) Descriptions Submitted to the FDA in SEND

Control Type (TCNTRL)	Count from FDA CDER Repository in SEND-submitted Datasets
Vehicle Control	1,895
Control	556
Vehicle	182
Reference Item	150
Control Article	128
Placebo Control	53
Positive Control	41
Saline Control	41
Control Article (Vehicle)	38
Negative Control	36
Water Control	19
Air Control	8
Untreated Control	8
NOT APPLICABLE	7
PEG Control	7
Formulation Buffer	6
Sham Control	6
Excipient	5
Untreated	5
SEE PROTOCOL	4
Water	4
2018-10-17T10:55:58	3
Absolute Control	3
Capsule Control	3
Citrate Buffer Control	3
Control Item	3
Dextrose Control	3
Dosed Control	3
Reference Control	3
Reference Control	3
Control (Vehicle)	2
Control Formulation	2
Excipient Control	2
NOT AVAILABLE	2
25 mM Sodium Citrate, 100 mM Sodium Chloride	1
Control HD	1
Control LD	1
Gel Vehicle Control	1
Health Screen/Sentinel	1
Mock-infected Control	1
NONE	1
Positive Control	1
Positive Control Item for the Micronucleus Test	1
Sham	1
Solution Vehicle Control	1

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