Clinical Study Data Reviewer's Guide

22nd Century Group, Inc.

Study CA24914

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Contents

1. Introduction

1.1 Purpose

This document provides context for tabulation datasets and terminology that benefit from additional explanation beyond the Data Definitions document (define.xml). In addition, this document provides a summary of SDTM conformance findings.

1.2 Acronyms

Acronym	Translation
WHO	World Health Organization
PK	Pharmacokinetic
MedDRA	Medical Dictionary for Regulatory Activities

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM IG v3.2
Controlled Terminology	CDISC SDTM CT 2018-03-30
Data Definitions	Define.xml (v2.0)
Medications Dictionary	WHO Dictionary Version 01SEP2017
Medical Events Dictionary	MedDRA 20.1
Pinnacle 21	Pinnacle 21 Community 2.2.0

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number:	CA24914	
Protocol Title:	A Longitudinal Ambulatory Study to Assess Changes in Cigarette Consumption Behavior and Biomarkers of Exposure during a 6-Week Switch to Very Low Nicotine Cigarettes	
Protocol Versions:	Final	09 May 2018
	Amendment 1	18 June 2018
	Amendment 2	20 July 2018

2.2 Trial Design Datasets

Are Trial Design datasets included in the submission? **Yes**

2.3.1 TA – Trial Arms

The Trial Arms (TA) dataset describes each planned arm in the trial. An arm is described as an ordered sequence of elements.

2.3.2 TE – Trial Elements

The Trial Elements (TE) dataset contains the definitions of the elements that appear in the Trial Arms (TA) dataset.

2.3.3 TV – Trial Visits

The Trial Visits (TV) dataset describes the planned Visits in a trial. Visits are defined as "clinical encounters" and are described using the timing variables VISIT, VISITNUM, and VISITDY.

2.3.5 TS – Trial Summary

The Trial Summary (TS) dataset details a summary of the trial in a structured format. Each record in the Trial Summary dataset contains the value of a parameter; a characteristic of the trial. Trial Summary is used to record basic information about the study such as trial phase, protocol title, and trial objectives as well as information about the planned and actual trial characteristics.

3. Subject Data Description

3.1 Overview

Are the submitted data taken from an ongoing study? **No**

If yes, describe the data cut or database status:

Were the SDTM datasets used as sources for the analysis datasets? **Yes**

If no, what were the sources of analysis datasets?

Do the submission datasets include screen failures? **Yes**

If yes, which datasets include screen failure data?

DM, DS, IE, SE, SV

Were any domains planned, but not submitted because no data were collected? **No**

If yes, list domains not submitted:

Are the submitted data a subset of collected data? **No**

If yes, describe the reason that all collected data were not provided:

Additional Content of Interest

Not Applicable.

3.2 Annotated CRFs

Please see acrf.pdf in the package.

The acrf.pdf included in the package has been dual-bookmarked by visit and domain. Each occurrence of a data collection module is bookmarked and annotated in full the first time it is used.

Annotation "[Not Submitted]" = data was not submitted per SDTM requirements.

3.3 SDTM Subject Domains

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
AE – Adverse Events		X		X		Events
CM – Concomitant Medication		X		X		Interventions
CO – Comments			X			Special Purpose
DA – Drug Accountability			X	X		Findings
DM – Demographics			X	X		Special Purpose
DS – Disposition			X	X		Events
EG – ECG Test Results		X		X		Findings
EX – Exposure			X	X		Interventions
FA – Findings About Events or Interventions			X			Findings
IE – Inclusion/Exclusion Criteria Not Met			X			Findings
LB – Laboratory Test Results		X		X		Findings
MH – Medical History			X			Events
PC – Pharmacokinetic Concentrations			X	X		Findings
PE – Physical Examination		X		X		Findings
PP – Pharmacokinetic Parameters			X			Findings
QS - Questionnaires			X	X		Findings
RP – Reproductive System Findings			X			Findings
SE – Subject Elements			X			Special Purpose
SU – Substance Use			X	X		Interventions
SV – Subject Visits			X			Special Purpose
VS – Vital Signs		X		X		Findings

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
XE – Investigational Product Exposure			X			Interventions
XT - Topography	X			X		Findings

3.3.1 AE – Adverse Events

In order to enable full traceability back to original Adverse Event responses as reported on the source CRF, source data values have been retained in SUPPAE for all data points detailed below. Per SDTM IG requirements Treatment Emergent Flag (AETRTEM) has also been submitted in SUPPAE.

QNAM	Description
ADMDTC	Hospitalization Admission Date
AECM001-010	Concomitant Medication #1-10 Given
AECMD001-010	Date Concomitant Med. #1-10 Given
AETRTEM	Treatment Emergent Flag
DISDTC	Hospitalization Discharge Date
LINKN001-010	Concomitant Med. #1 - 10 Link Number

3.3.2 CM – Concomitant Medications

WHO dictionary variables have been retained in SUPPCM to provide full access to ATC Codes/Text.

QNAM	Description
AEID	AE ID
ATCCODE1	WHO ATC Code – Level 1
ATCCODE2	WHO ATC Code – Level 2
ATCCODE3	WHO ATC Code – Level 3
ATCCODE4	WHO ATC Code – Level 4
ATCTEXT1	WHO ATC Text – Level 1
ATCTEXT2	WHO ATC Text – Level 2
ATCTEXT3	WHO ATC Text – Level 3
ATCTEXT4	WHO ATC Text – Level 4
DRRCNO	WHO Drug Record Number
DRSEQ1	WHO Drug Seq 1
DRSEQ2	WHO Drug Seq 2
MHID	MH ID
TRADNAME	WHO Trade Name

3.3.3 DA – Drug Accountability

Supplemental information pertaining to product return has been submitted in SUPPDA.

QNAM	Description
ADINFO	Additional Information Collected?
ADINFOSP	Additional Information Specified
BUTTRET	Cigarette Butts Returned
CONSMAMT	Consume Other Cigarettes Amount
CONSUME	Consume Cigarettes Other than Reported?
CONSUMFQ	Consume Other Cigarettes Frequency
NONVLNBR	Non-VLN Butts Returned
UBSPEC	Usual Brand Specified
VISDTC	Visit Date

3.3.4 DM – Demographics

Where subjects selected 'Other' race, the other race has been specified in SUPPDM.

QNAM	Description
RACESPEC	Other Race Specify

3.3.5 DS – Disposition

Supplemental information pertaining to subject disposition has been submitted in SUPPDS.

QNAM	Description
ACTIVE	Active
ASGNPROD	Assigned Product
ENROLDTC	Enrolled Date
ENROLLED	Enrolled
PATCAPTN	Patient Caption

QNAM	Description
PROTVER	Protocol Amendment Number
RANDNO	Randomization Number
RCPRTVER	Protocol Amendment Number Re-consent

3.3.6 EG – ECG Test Results

Clinical Significance has been submitted in SUPPEG.

QNAM	Description
EGCLSIG	ECG Clinical Significance

3.3.7 EX – Exposure

Original electronic diary collection date/time has been provided in SUPPEX.

QNAM	Description
COLDTC	Daily Diary Collection Date/Time

3.3.8 LB – Laboratory Test Results

To enable full traceability back to original Clinical Laboratory responses as reported at Source, data values have been retained in SUPPLB for all data points detailed below.

QNAM	Description
LBCLSIG	Clinical Significance Flag
VISDTC	Planned Visit Date

3.3.9 PC – Pharmacokinetic Concentrations

To facilitate downstream TFL programming, source data values have been retained in SUPPPC for all data points detailed below.

QNAM	Description
ACTHOUR	Actual Time from Reference Dose (h)
POINT	A Seq Number Assigned to Nominal Times
UCPERF	Was the Sample Collected
VOIDLOST	Was any void lost in this 24hr period?
VOLUME	Urine Sample Volume
VOLUNIT	Urine Sample Volume Unit

3.3.10 PE – Physical Examination

Supplemental information pertaining to physical examination has been submitted in SUPPPE.

QNAM	Description
PECLSIG	Clinical Significance
PESYMP	Reported Symptom
VISDTC	Visit Date

3.3.11 QS – Questionnaires

Supplemental information pertaining to questionnaires has been submitted in SUPPQS.

QNAM	Description
DATASET	Questionnaire Dataset
SCALE	Questionnaire Scale
VENDOR	Questionnaire Vendor

3.3.12 SU – Substance Use

To enable full traceability back to original substance use responses as reported at Source, data values have been retained in SUPPSU for all data points detailed below. .

QNAM	Description
BRAND	Usual Brand
DURATION	Duration of Cigarette Use
DURUNIT	Duration Unit
FLAVOR	Usual Brand Flavor
SIZE	Usual Brand Size
STYLE	Usual Brand Style

3.3.13 VS – Vital Signs

Clinical Significance has been submitted in SUPPVS.

QNAM	Description
VSCLSIG	Vital Signs Clinical Significance

3.3.14 XT– Topography

Supplemental information pertaining to topography data has been submitted in SUPPXT.

QNAM	Description
CIGHOLD	Cigarette Holder
CIGID	Cigarette Identifier
CONSMORN	Consumed Since Morning
USUALCIG	Usual Cigarette

4. Data Conformance Summary

4.1 Conformance Inputs

Was Pinnacle 21 used to evaluate conformance? **Yes**

If yes, specify the versions of Pinnacle 21 and the Pinnacle 21 validation rules:

SDTM IG 3.2, Pinnacle 21 Community Validation 2.2.0

Were sponsor-defined validation rules used to evaluate conformance? **No**

If yes, describe any significant sponsor-defined validation rules:

Were the SDTM datasets evaluated in relation to define.xml? **Yes**

Was define.xml evaluated? **Yes**

Provide any additional compliance evaluation information:

Not Applicable

4.2 Issues Summary

Dataset	Diagnostic Message	Severity	Count	Explanation
AE	Epoch value not found in 'Epoch' extensible codelist	Warning	67	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
AE	Missing values for AESTDTC, AESTRF and AESTRTPT, when AEENDTC, AEENRF or AEENRTPT is provided	Warning	3	Start Date/Time of AE is unknown however the End Date/Time is known.
AE	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
CM	Epoch value not found in 'Epoch' extensible codelist	Warning	37	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
CM	Missing Start Time-Point value	Warning	5	Start Date/Time and End Date/time of conmeds are unknown.
CM	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
DA	Epoch value not found in 'Epoch' extensible codelist	Warning	581	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
DA	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.

Dataset	Diagnostic Message	Severity	Count	Explanation
DM	RACE value not found in 'Race' extensible codelist	Warning	13	In the event of a subject selecting two or more races on the CRF, the SDTM IG states that Race should be mapped to MULTIPLE in the parent DM domain, with the individual races making up the "multiple" race being mapped to SUPPDM. OTHER and UNKNOWN are not a match to Controlled Terminology however the 'Race' code list is extensible.
EG	EGTEST value not found in 'ECG Test Name' extensible codelist	Warning	5	Where a full panel of ECG Tests is not collected, guidance recommends that all tests be collapsed into one test. "ECG Data" is not a match to CDISC Controlled Terminology however the 'ECG Test Name' code list is extensible.
EG	EGTESTCD value not found in 'ECG Test Code' extensible codelist	Warning	5	Where a full panel of ECG Tests is not collected, guidance recommends that all tests be collapsed into one test. "EGALL" is not a match to CDISC Controlled Terminology however the 'ECG Test Code' code list is extensible.
EG	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
EX	Epoch value not found in 'Epoch' extensible codelist	Warning	10966	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.

Dataset	Diagnostic Message	Severity	Count	Explanation
EX	EX record is present, when subject is not assigned to an arm	Warning	38	Subjects who participated in the product trial are included in EX despite not eventually being randomized.
EX	Exposure end date is after the latest Disposition date	Warning	40	Source disposition date is not the date of last contact for all subjects.
FA	Epoch value not found in 'Epoch' extensible codelist	Warning	208	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
FA	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
IE	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
IE	Missing IEDY variable, when IEDTC variable is present	Warning	1	Since subjects included in the IE domain were not randomization, IEDY cannot be derived since these subjects do not have a RFSTDTC.
LB	EPOCH value not found in 'Epoch' extensible codelist	Warning	2548	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
LB	LBORRESU value not found in 'Unit' extensible codelist	Warning	69	"s/co ratio" is not a match to CDISC Controlled Terminology however the 'Unit' code list is extensible.
LB	LBSTRESU value not found in 'Unit' extensible codelist	Warning	69	"s/co ratio" is not a match to CDISC Controlled Terminology however the 'Unit' code list is extensible.

Dataset	Diagnostic Message	Severity	Count	Explanation
LB	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
MH	Missing values for MHSTDTC, MHSTRF and MHSTRTPT, when MHENDTC, MHENRF or MHENRTPT is provided	Warning	2	Start Date/Time of medical history is unknown however the End Date/Time is known.
MH	Model permissible variable added into standard domain	Warning	3	VISIT and VISITNUM have been added to provide clarification of timing of collection. EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
PC	EPOCH value not found in 'Epoch' extensible codelist	Warning	6323	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
PC	PCORRESU value not found in 'Unit' extensible codelist	Warning	9659	Pinnacle 21 erroneously validates PCORRESU against the UNIT Code List (C71620) rather than the PKUNIT Code List (C85494). "ng/mL" can be found on the PKUNIT Code List.
PC	PCSTRESU value not found in 'Unit' extensible codelist	Warning	9659	Pinnacle 21 erroneously validates PCSTRESU against the UNIT Code List (C71620) rather than the PKUNIT Code List (C85494). "ng/mL" can be found on the PKUNIT Code List.

Dataset	Diagnostic Message	Severity	Count	Explanation
PC	Model permissible variable added into standard domain	Warning	2	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'. PCENDY has been added to capture the end day of Urine Interval concentrations.
PE	EPOCH value not found in 'Epoch' extensible codelist	Warning	14	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
PE	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'
PP	EPOCH value not found in 'Epoch' extensible codelist	Warning	1689	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
PP	Model permissible variable added into standard domain	Warning	4	VISITDY, VISITNUM and VISIT have been included to provide clarification on timing of parameters. EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
QS	EPOCH value not found in 'Epoch' extensible codelist	Warning	9887	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.

Dataset	Diagnostic Message	Severity	Count	Explanation
QS	QSCAT value not found in 'Category of Questionnaire' extensible codelist	Warning	17151	"FAGERSTROM", "MNWS-R", "PERCEIVED HEALTH RISK SCALE" and "QSU-BRIEF" are not a match to CDISC Controlled Terminology however the 'Category of Questionnaire' code list is extensible.
QS	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
RP	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'.
SE	EPOCH value not found in 'Epoch' extensible codelist	Warning	127	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
SE	Model permissible variable added into standard domain	Warning	2	SESTDY has been provided according to rule SD1087 which states 'Study Day of Start (--STDY) variable should be included into dataset, when Start Study Date/Time (--STDTC) variable is present.' Similarly SEENDY has been provided according to rule SD1091.

Dataset	Diagnostic Message	Severity	Count	Explanation
SU	Model permissible variable added into standard domain	Warning	3	SUDTC has been included to provide clarification of timing of collection. SUDY has been provided according to rule SD1087 which states 'Study Day of Start (--STDY) variable should be included into dataset, when Start Study Date/Time (--STDTC) variable is present.' EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'
SV	EPOCH value not found in 'Epoch' extensible codelist	Warning	370	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
SV	Model permissible variable added into standard domain	Warning	1	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'
TA	EPOCH value not found in 'Epoch' extensible codelist	Warning	4	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
TS	Model permissible variable added into standard domain	Warning	2	TSVAL1 and TSVAL2 have been included to display continuation of TSVAL
VS	EPOCH value not found in 'Epoch' extensible codelist	Warning	2127	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.

Dataset	Diagnostic Message	Severity	Count	Explanation
VS	VSTEST value not found in 'Vital Signs Test Name' extensible codelist	Warning	9	Where a full panel of Vital Signs Tests is not collected, guidance recommends that all tests be collapsed into one test. "Vital Signs Data" is not a match to CDISC Controlled Terminology however the 'Vital Signs Test Name' code list is extensible.
VS	VSTESTCD value not found in 'Vital Signs Test Code' extensible codelist	Warning	9	Where a full panel of Vital Signs Tests is not collected, guidance recommends that all tests be collapsed into one test. "VSALL" is not a match to CDISC Controlled Terminology however the 'Vital Signs Test Code' code list is extensible.
VS	Model permissible variable added into standard domain	Warning	2	EPOCH has been included according to rule SD1077 which states 'Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH'. VSEVLINT has been provided to capture number of minutes in test position where applicable.
XE	EPOCH value not found in 'Epoch' extensible codelist	Warning	82	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
XT	EPOCH value not found in 'Epoch' extensible codelist	Warning	7462	"PRODUCT EXPOSURE" is not a match to CDISC Controlled Terminology however the 'Epoch' code list is extensible.
XT	XTORRESU value not found in 'Unit' extensible codelist	Warning	10770	"mJ", "mmWG/(mL/sec)" and "mmWg" are not a match to CDISC Controlled Terminology however the 'Unit' code list is extensible.

Dataset	Diagnostic Message	Severity	Count	Explanation
XT	XTSTRESU value not found in 'Unit' extensible codelist	Warning	10770	"mJ", "mmWG/(mL/sec)" and "mmWg" are not a match to CDISC Controlled Terminology however the 'Unit' code list is extensible.
DEFINE	Invalid Term in Codelist 'No Yes Response'	Warning	1	This appears to be a Pinnacle 21 Bug. The flagged value 'N' is a valid term in the 'No Yes Response' Code List. The Pinnacle 21 forum states that this bug will be fixed in the next release of the validator.
DEFINE	Invalid Term in Codelist 'Relation to Reference Period'	Warning	1	This appears to be a Pinnacle 21 Bug. The flagged value 'ONGOING' is a valid term in the ''Relation to Reference Period' Code List. The Pinnacle 21 forum states that this bug will be fixed in the next release of the validator.