National Cancer Institute (NCI)

Clinical Data Interchange Standards Consortium (CDISC) Best Practices Document

v.1
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DOCUMENT HISTORY

Version	Release Date	Summary of Changes	Author/ Changes Made By
0.1	10/14/2018	Initial Draft	Samuel Isa
0.1	11/26/2018	Updated, added new workflows	Brenda Maeske, Mary Cooper
0.1	02/28/2019	Added additional Best Practices content, diagrams	Samuel Isa
0.1	03/01/2019	Edited and reviewed by SME	Shannon Labout
0.1	03/05/2019	Final Review	Neesha Desai

TABLE OF CONTENTS

1. PURPOSE

The purpose of this policy is to describe, and make consistent, the processes and practices associated with the NCI's transition of their current Network Rave Data Standards (NRDS) Initiative, led by the Cancer Therapy Evaluation Program (CTEP), into a CDISC-centric implementation. This artifact will document business process improvement activities and assessment.

2. BACKGROUND

The Food and Drug Administration (FDA) has mandated that clinical trial sponsors whose studies start after Dec 17, 2016, must submit their clinical study data sets in the Study Data Tabulation Model (SDTM) standard format. For Investigational New Drugs (INDs), the requirement applies for studies that start after Dec. 17, 2017. SDTM provides a standard for organizing and formatting data to streamline the process in collection, management, analysis and reporting. CDISC is a global nonprofit standards development organization with a worldwide team of staff and volunteer experts across the medical community. CDISC provides data standards to streamline clinical research, including the SDTM.

The NCI is working in collaboration with CDISC to collect data in the Clinical Data Standards Harmonization (CDASH) format for the Oncology Patient Enrollment Network System (OPEN), Clinical Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) and the Clinical Data Update System (CDUS). According to the FDA Study Data Conformance Guide, section 4.1.2 (SDTM General Considerations), it is recommended that sponsors implement the SDTM standard for representation of the clinical trial tabulation data prior to the conduct of the study. The use of case report forms that incorporate CDASH standard data elements allows for a more simplified process for the creation of the SDTM domain.

3. AUTHORITY

NCI's CTEP's mission is to improve the lives of cancer patients by finding better ways to treat, control and cure cancer. CTEP accomplishes this mission by funding an extensive national program of cancer research and by sponsoring clinical trials to evaluate new anti-cancer agents. These sponsored clinical trials are required to abide by the regulations set forth by the FDA and as a result, have chosen to implement the effort to move to using CDASH and SDTM as the respective collection and submission standards for clinical data contained in the aforementioned clinical trials.

4. GUIDING PRINCIPLES and STANDARDS

The following high-level principles will guide the efforts related to this project:

1. CDISC CDASH establishes a standard way to collect data in a similar way across studies and sponsors so that data collection formats and structures provide clear

traceability of submission data into the Study Data Tabulation Model (SDTM), delivering more transparency to regulators and others who conduct data review.[1]

2. CDISC CDASH is used for the data classification of different data collection fields and is the data collection standard preferred for NCI sponsored studies, however CDASH is not mandated by the FDA as such
3. CDISC SDTM is used as both a measure of compliance and to provide guidance, and further is the submission standard that is mandated by the FDA applicable to:
    a. Annotated Case Report Forms (CRFs)
    b. Supplemental Data Definitions
    c. Datasets
    d. Value Level Metadata
    e. Controlled Terminology
    f. Computational Algorithms
4. All CTEP IND (Investigational New Drug) studies activated after 1/1/2020 shall be CDISC compliant, this date will be assessed based on LPO Impact Analysis
5. Current Scope of CDISC Global Library Beta Release
    a. CDISC CDASHv2.0
    b. CDISC Controlled Terminology Package 36 (2018-12-21)
    c. SDTM v3.3

5. BEST PRACTICES

The following concepts and definitions are integral to guiding the development of the NCI CDISC Implementation effort.

Common Data Elements Best Practices

1. Eligibility Checklist Forms (ECh)- Form Questions can have 3 different types of CDEs
    a. CDASH CDISC Library Data Elements (already curated)
    b. Inclusion/Exclusion Criteria
    c. Supplemental Question (not already curated CDASH elements)
2. CDASH provides the IETEST and IETESTCD variables for individual inclusion/exclusion questions. CDASH does not provide the Inclusion/Exclusion criteria values, which need to set up per study, and the set up of a global CT list to make these more consistent.
    a. It is suggested to not curate these unless the LPOs want to use the CDASH Controlled Vocabulary standard for Permissible Values (PVs)
3. For curation CDISC details are needed – LPOs provide map to SDTM, including:
    a. Variable label
    b. Variable name
    c. Data format
    d. List of values (if enumerated)
4. CDASH CDEs

[1] https://www.cdisc.org/standards/foundational/cdash

a. CDISC approved NCI Implementation of CDISC Library variables
b. CBIIT will curate future SDTM CDEs as requested by LPOs based on data submission
c. Eligibility Criteria (IETEST and IETESTCD)
    i. Curated by CBIIT caDSR curator teams for NCTN/ETCTN LPOs
    ii. Allow LPOs to keep existing libraries of IETEST codelists
d. Date datatype limited to 11 characters (non-specific display format)
e. Non-enumerated CDEs
    i. Should have asset reasonable max length based on expected data
    ii. Text based CDEs have a 200 character limit
f. Enumerated CDEs max length based on CDASH/SDTM controlled terminology
g. Found in the caDSR CDE Browser- folder path: All NCI Standards > Classifications > CDISC (NCI Implementation) > CDASH 2.0 then click on specific CDASH domains to view curated CDEs for the domain

Rave Global Library Best Practices

1. CTSU Process
    a. CDASH domain forms are built in the caDSR FormBuilder
    b. CDASH domain forms are imported from the caDSR into Rave via OCI
    c. Rave Study Build Activities are managed
    d. CDISC Global Library ALS is created
    e. Compliance review managed for CDISC Rave GLIB ALS
    f. Finalized CDISC Rave GLIB ALS is provided to LPOs
2. Rave study data will have to be transformed by LPOs during SDTM file generation by SAS programs
3. Post initial implementation, new versions of CDISC SHARE will be managed at the CDISC GLIB level by CTSU and at the Seed study eCRF level by LPOs
4. Processes for LPOs and ECh forms across OPEN and Rave
    a. Use existing CDEs during caDSR formbuilding activities
    b. Curate new CDEs in the caDSR as needed
    c. Build ECh forms in the caDSR
    d. Import ECh forms into Rave using the OCI
    e. All ECh forms and questions must be CDISC compliant
    f. Max length and date data type will need to be specified during curation activities for all ECh CDEs

Electronic Case Report Form (eCRF) Build Best Practices

1. Rave eCRFs may have different build scenarios. Please refer to the NCI CDISC Rave GLIB Release Notes for details.
    a. Variables from a single domain.
    b. Variables from multiple domains.
    c. Custom variables and CDASH/SDTM

TAC/TAD/ARM and other Study Design/Dosing Best Practices

1. TAC – Treatment Assignment Code
    a. Short identifier (10 characters or less) of study treatment used for CTEP CORE IT system to system communications. Protocol specific
2. TAD – Treatment Assignment Descriptor
    a. Abbreviated depiction of a patient's therapy to enhance human interface to differentiate different study therapies (not ARMS) during data collection and analysis by CTEP
    b. Focus is on study variable. The TAD should NOT be designed to level of detail to support patient care.

3. In SDTM, an ARM is a brief description of entire planned path through the study
    a. All of the potential ARMs are described in the text of the protocol
    b. In cases where ARMs cannot be fully described in advance - wait until all subjects have completed the study to create the SDTM ARM and ARMCD values
4. It is not possible to create complete Trial Design domains prior to the study if the protocol has indefinite numbers of
    a. repeating Elements - (however, you should still be able to populate Trial Elements (TE) in advance if all of the possible treatments are described in the Protocol)
    b. Visits (affects Trial Visits – (TV) and all visit based data for subjects)
    c. Epochs (Steps) (affects Trial Arms - TA and subject-level data)
    d. Arms (Treatment Strategies) (affects Trial Arms TA & Demographics DM)
5. Preparation for the completion of Trial Design domains can still be done by:
    a. setting up standard Elements in Trial Elements (TE) for all possible treatments and other "states of being"
    b. building your Trial Visits (TV) domain as the study progresses
    c. Building a standard set of EPOCHs to be used in the study and in Trial Design
6. ARM/ARMCD are created in Trial Arms (TA.xpt) and used in Demographics (DM.xpt)
7. VALUES for ARM/ARMCD in DM HAVE TO MATCH the values for ARM/ARMCD created in Trial Arms (TA.XPT) domain
    a. The same values are also used to populate ACTARM and ACTARMCD in Demographics
8. Whether or not SDTM concepts of Trial Arms and Trial Elements are adopted into your data flow, move toward putting individual study information into the SDTM Trial Design structures early in the process to increase your organizational understanding of these important SDTM domains.
9. Those domains include Trial Arms (TA), Trial Elements (TE), Trial Inclusion/Exclusion Criteria (TI), Trial Visits (TV) and Trial Summary (TS)
10. Values from most of these domains are used in subject level data, so having these domains set up prior to the study makes that "controlled terminology" (e.g., IETEST, VISIT) available for the collection of subject data.

11. Continue simplification of TAC/TAD so a given study has a set of unique, meaningful >/= 200 character descriptions of each treatment and other "states of being" that occur in the study (e.g., SCREENING), which can then be used to create Trial Elements (TE) and Trials Arms (TA)
12. To the extent possible, standardize and reuse these across studies where they are truly the same. At least establish pattern-based naming conventions.

6. FREQUENTLY ASKED QUESTIONS

The following table contains commonly discussed questions and answers related to the NRDS to CDISC implementation:

Topic#	Question/ITEM	Response
1	What content must be CDISC CDASH compliant?	All CTEP IND studies activated after 1/1/2020 shall be CDISC compliant.
2	What content must be CDISC SDTM compliant?	While not all data collected will need to be reported (e.g. safety data), all reported content as defined by the FDA submission standard must be compliant.
3	What actions are needed (from an NCI perspective) if a Common Data Element (CDE) is not required by CDISC?	If the CDE is not a required CDISC standard and is needed in your study, submit the request to the NCI CDISC Harmonization WG (ncicdiscsupport@nih.gov) for consideration as a CDISC standard.
4	What actions are needed to make a 'partial match' CDE compliant with CDISC CDASH requirements?	Use the CDISC CDASH and SDTM supplemental guides to create a new CDISC CDASH compliant CDE.
5	What fields need to match for a CDE to be CDISC CDASH compliant?	All fields should match all CDISC variables to minimize compliance issues during submission.
6	Does a CDE with no match to CDISC CDASH/ SDTM require manual creation based on the CDISC CDASH/ SDTM guides?	Yes; create a new CDE that matches the CDISC CDASH requirements. Contact ncicdiscsupport@nih.gov for additional CDE curation.
7	What about the CDISC standards that are not geared towards oncology trials?	CDISC has developed 4 Oncology Standards: Breast, Prostate, Colorectal and Lung. NCI can propose additional domains as needed.
8	What is the burden of CDISC compliance on legacy trials?	Legacy Trials are not impacted by the CDISC Implementation
9	What is the burden of CDISC compliance on new trials?	NCI will follow FDA requirements. Any required data being reported to the FDA for new trials needs to be CDISC compliant..

10	How are potential differences between CDUS Complete reporting versus CDASH requirements to be managed?	NCI is aware of the various reporting requirements and these will be addressed during impact analysis and implementation activities.

7. Process Flows

The processes below have been created to provide support in the NCI CDISC Implementation effort.

LPO Management of Supplemental Questions (Supplemental Qualifiers in SDTM) Workflow

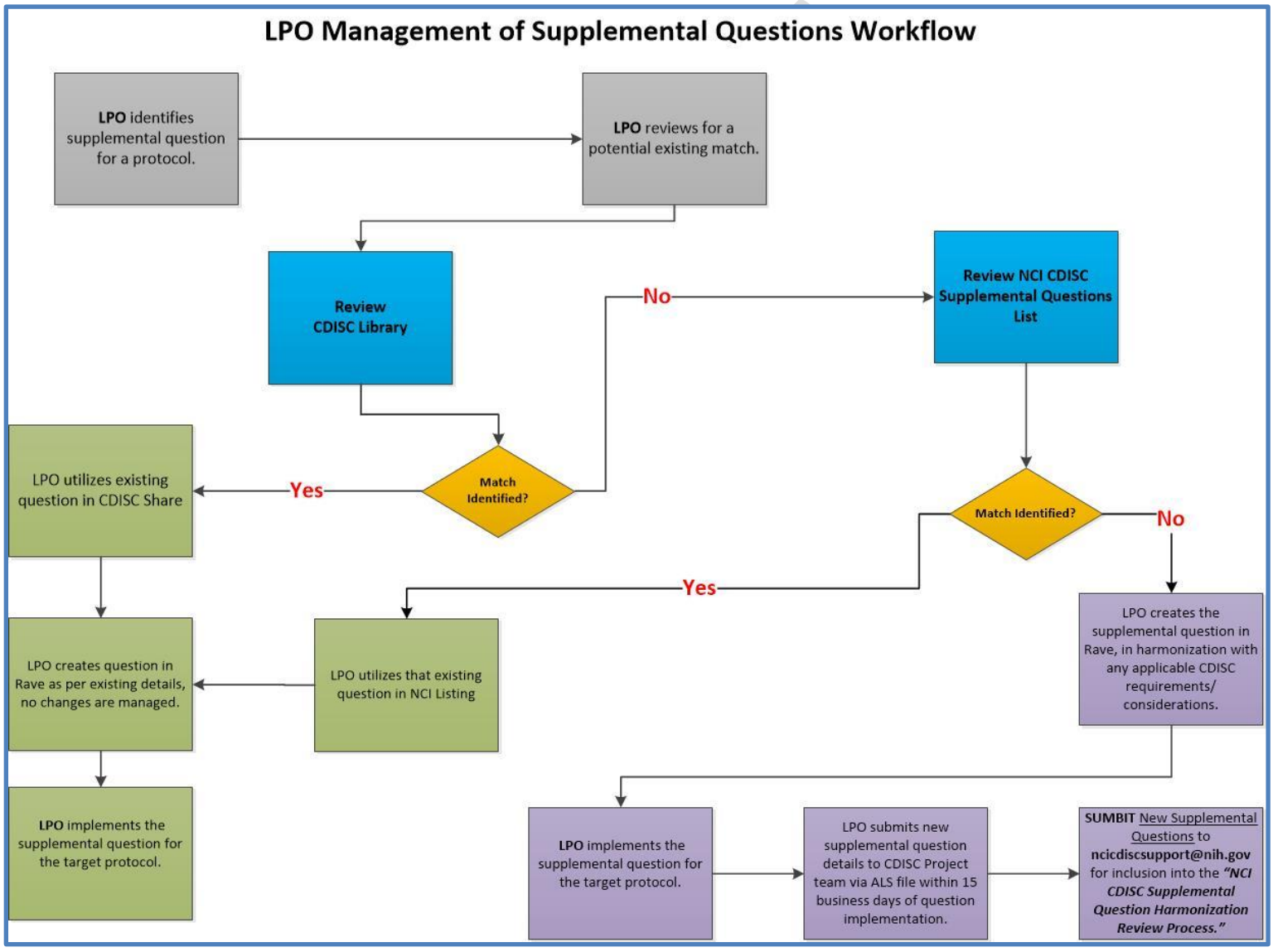

Figure 1: LPO Management of Supplemental Questions (Supplemental Qualifiers in SDTM) Workflow

NCI CDISC Supplemental Question Harmonization Review Workflow

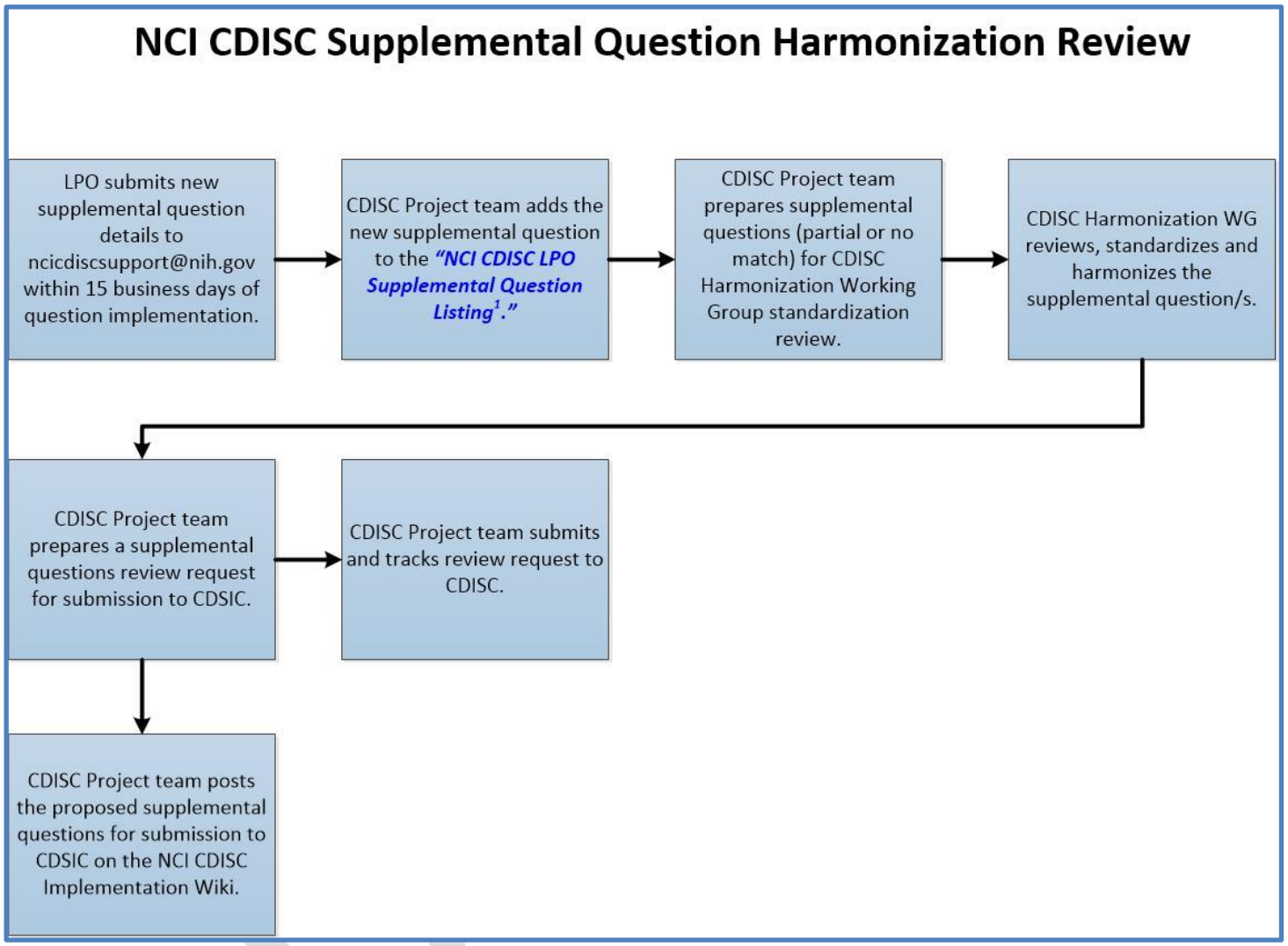

Figure 2: NCI CDISC Supplemental Question Harmonization Review Workflow

CDISC Implementation Workflow

The following workflow provides a process for the LPOs to implement and manage the Rave GLIB CDISC Global Library. Note that all new CDEs curation for this effort will have support from the NCI CDISC SME.

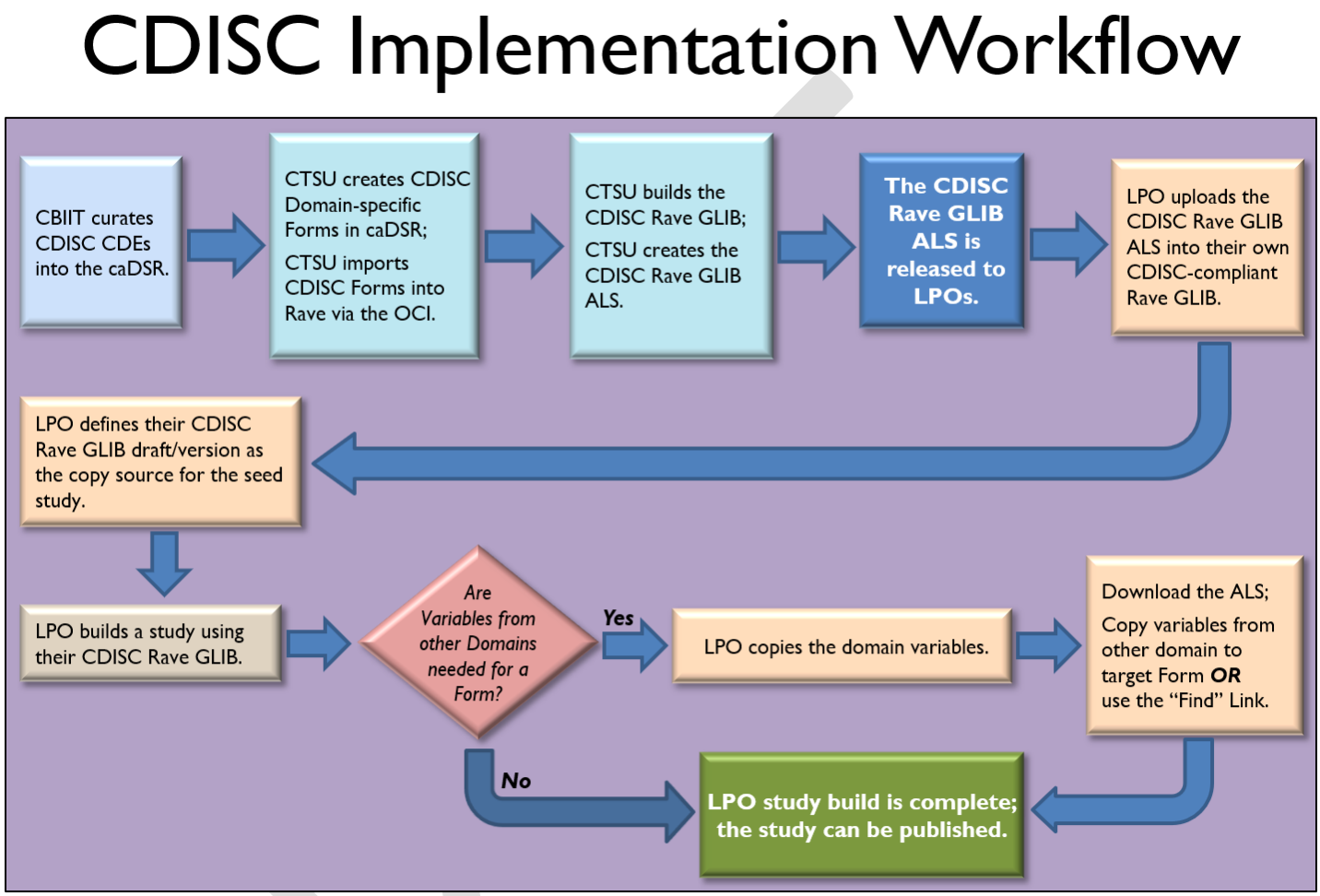

Figure 3: Figure 2: NCI CDISC Supplemental Question Harmonization Review Workflow

8. Acronyms, Abbreviations and Initialisms

ALS	Architect Loader Specification
ARM	
ARMCD	
caDSR	Cancer Data Safety Repository
CDASH	Clinical Data Standards Harmonization
CDE	Common Data Elements
CDISC	Clinical Data Interchange Standards Consortium
CDUS	Clinical Data Update System
CM	Concomitant Medication
CTEP-AERS	Clinical Therapy Evaluation Program Adverse Event Reporting System
CRF	Case Report Form
CTSU	Clinical Trial Support Unit
DA	Drug Accountability domain
EC	Exposure as Collected
ECh	Eligibility Checklist
EX	Exposure
FDA	Food and Drug Administration
GLIB	Global Library
IA	Impact Analysis
IND	Investigational New Drug
LPO	Lead Protocol Organizations
MTD	Maximum Tolerated Dose
NRDS	Network Rave Data Standards
OCI	Forms importer to caDSR
OID	Organizational Identification
OPEN	Oncology Patient Enrollment Network
PTD	Protocol Treatment Description (parent term assigned at study level)
PV	Permissible Values
SDTM	Study Data Tabulation Model
TA	Trial Arms
TAC	Treatment Assignment Code
TAD	Treatment Assignment Descriptor
TE	Trial Elements
TI	Trial Inclusion
TV	Trial Visits