Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH)

Guidance for Industry

Technical Specifications Document

For questions regarding this technical specification document, contact CDER at cder-edata@fda.hhs.gov.

U.S. Department of Health and Human Services
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Revision History

Date	Version	Summary of Revisions
August 2021	1.0	Initial Version
January 2022	1.1	Section 5.0 – Added language about CDISC Controlled Terminology Revisions made to Section 5.1.4 - Corrected test code values for Ascites and Encephalopathy Grade.

Table of Contents

Contains Nonbinding Recommendations

Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Nonalcoholic Steatohepatitis (NASH)

Guidance for Industry
Technical Specifications Document[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

1.0 Introduction

Nonalcoholic steatohepatitis (NASH) is a subcategory of nonalcoholic fatty liver disease (NAFLD). NASH carries a significant disease burden as it can progress to cirrhosis and liver failure and is associated with an increase incidence of liver cancer. Currently, the U.S. Food and Drug Administration (FDA) has not approved any therapies for NASH.

The Division of Hepatology and Nutrition (DHN) serves as the clinical review division in the Office of New Drugs (OND) for review of drug products for treatment of liver fibrosis due to NASH. In December 2018, FDA issued a draft guidance outlining recommendations for clinical development of drugs intended for treatment of noncirrhotic NASH with liver fibrosis.[2] The 2018 draft guidance for industry acknowledges that subjects with NASH fibrosis have unique challenges (e.g., underlying hepatic dysfunction) during drug development. Furthermore, evaluation of potential drug-induced liver injury (DILI) in this population is challenging because the risk of DILI in subjects with underlying liver disease has not been fully characterized and it can be difficult to differentiate between progression of liver disease and DILI.

This document provides detailed information and specifications for the content of the tabulated domains and analysis data sets submitted to FDA as part of the sponsor's/applicant's application for drugs intended to treat noncirrhotic NASH. This guidance does not provide recommendations

[1] This guidance has been prepared by the Division of Hepatology and Nutrition in the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2018-D-1216 (available at https://www.regulations.gov/docket?D=FDA-2018-D-1216) (see the instructions for submitting comments in the docket).

[2] See the draft guidance for industry *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

for clinical development of drugs intended for treatment of NASH, or assessment of potential DILI.

The recommendations outlined in the guidance pertain to submission of the sponsor's tabulated and analysis data sets in order to improve reviewability. These specifications also provide an opportunity for dialogue between the sponsor and DHN to discuss issues related to trial design or conduct that may affect the content of these data sets. These specifications are intended to support the draft guidance for industry *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment*[2] (NASH Guidance) and reflect the data standards and processes described in the FDA *Study Data Technical Conformance Guide*.[3]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

2.0 Relevant Acronyms

Abbreviation	Description
ADaM	Analysis Data Model
ADRG	Analysis Data Reviewers Guide
APRI	Aspartate Aminotransferase-to-Platelet Ratio Index
BDS	Basic Data Structure
CAC	Cardiac Adjudication Committee
CDISC	Clinical Data Interchange Standards Consortium
CK-18	Cytokeratin-18
CRN	Clinical Research Network
DHN	Division of Hepatology and Nutrition
DILI	Drug-Induced Liver Injury
ELF	Enhanced Liver Fibrosis
FDA	Food and Drug Administration
HAC	Hepatic Adjudication Committee

[3] Available at https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Abbreviation	Description
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic Steatohepatitis
NCI EVS	National Cancer Institute Enterprise Vocabulary Services
OCCDS	Occurrence Data Structure
PRO-C3	N-terminal propeptide of type III collagen
RELREC	Related Records Domain
SDRG	Study Data Reviewers Guide
SDTM	Study Data Tabulation Model
SMQ	Standardized MedDRA Query
TAUG	Therapeutic Area User Guide

3.0 FDA Data Standards Catalog

This technical specification has been drafted in accordance with the currently supported versions of the Study Data Tabulation Model (SDTM) Implementation Guide and Analysis Data Model (ADaM) Implementation Guide as noted in the FDA Data Standards Catalog.[4] As new versions of the respective implementation guides become available and supported by FDA, this technical specification may change to align to the newly supported implementation guide(s).

Sponsors should review the FDA Data Standards Catalog to ensure data submissions follow FDA-supported standards.

4.0 Overview of Data Sets

This technical specification contains guidance for 20 data sets (14 SDTM domains and 7 ADaM data sets) relevant to noncirrhotic NASH development programs briefly described below. The subsequent sections provide more detailed descriptions regarding the information to be collected and stored in each domain and/or data set. Sponsors should submit all required data sets, including those not discussed in this technical specification.

[4] Available at https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

4.1 SDTM Domains

This technical specification provides guidance for providing 14 SDTM domains. Sponsors should still provide standard SDTM domains in addition to those listed below, including but not limited to Demographics (DM), Adverse Events (AE), Disposition (DS), Death Details (DD), Subject Visits (SV), Exposure (EX), Comments (CO), etc.

Biospecimen Events (BE) domain: This domain contains information related to the collection of biological specimens. It is an events domain structured as one record per biospecimen event per biospecimen identifier per subject, and links to the Biospecimen Findings (BS) domains.

Biospecimen Findings (BS) domain: This findings domain contains information related to observations of specimen quality and characteristics of collected biospecimens. This information is collected to assess the adequacy of the biopsies that are used for analysis and is structured as one record per measurement per biospecimen identifier per subject.

Microscopic Findings (MI) domain: This domain contains all information related to histologic characteristics of liver biopsies. This domain is structured as a Clinical Data Interchange Standards Consortium (CDISC) findings domain and is structured as one record per subject per test per collection.

Supplemental Microscopic Findings (SUPPMI) domain: This domain contains supplemental information related to the biopsies, specifically the sponsors' assessment of slide adequacy. Justification should be provided in this domain for specimens deemed inadequate.

Disease Response and Clinical Classifications (RS) domain: This domain contains information related to disease response to therapy that includes clinical classification based on published criteria and captures results of Model for End-Stage Liver Disease (MELD) scoring[5] and Child-Pugh Classification. This findings domain is structured as one record per response or clinical classification assessment timepoint per visit per subject per assessor per medical evaluator.

Imaging Results (ZI) domain: This custom domain contains results of imaging procedures done to assess liver steatosis, inflammation, and fibrosis. Sponsors may choose the tests and data points to collect from imaging procedures, but this domain provides guidance to ensure the data is submitted to the FDA in a consistent manner.

Adjudication (ZA) domain: This domain contains results of assessments of individual adjudicators as it pertains to potential DILI and other clinical events and outcomes. This domain is structured similar to the MI domain, where the evaluator information is stored in ZAEVAL and ZAEVALID to account for intra- and inter-observer variability.

[5] Individual components of MELD scoring are captured elsewhere, but final calculation for MELD is placed in the RS domain.

Additional information, instructions, and CDISC Controlled Terminology are included in individual subsections pertaining to the Concomitant Medications (CM), Medical History (MH), Laboratory (LB), Microbiology Specimens (MB), Substance Use (SU), and Trial Summary (TS) domains.

4.2 ADaM Data Sets

ADaM data sets include variables that represent derived study days. It is assumed that the anchor date for study day 1 is Date of First Exposure to Treatment (TRTSDT) and this date of first dose is identical to Date of Randomization (RANDDT). If the Date of First Exposure to Treatment and Date of Randomization differ, sponsors should provide an explanation for this discrepancy. All ADaM data sets should be accompanied by informative metadata, as provided in a compliant ADaM define.xml document and Analysis Data Reviewers Guide (ADRG) that describes the source and derivation of the variables. In addition, programs used to create ADaM data sets should be submitted.

Subject-Level Analysis Data Set (ADSL): This data set contains one record per subject. This data set provides information about the subjects' demographics, treatment arm, trial start and end dates, and summary baseline characteristics. Many of the baseline characteristic variables in this data set are calculated or derived values from other data sets (e.g., baseline alanine aminotransferase (ALT)) and an associated categorization of that value. The notes in the ADSL table provided within this document should be considered a guide and a baseline instruction set; sponsors should submit additional variables and derivations as they see fit. Specific sections of the ADSL should be carried into other ADaM data sets for analysis purposes (e.g., Basic Demographic Variables, Treatment Arms, etc.), and are noted in the full description of the ADaM data sets. All derivations should be noted in the define.xml file, and additional notes about the data set included in the ADRG.

Adverse Event Analysis Data Set (ADAE): This data set contains one record per adverse event (AE) per subject. All AEs reported for a subject during their participation in the trial should be recorded. It also includes additional variables and specific derivations requested by the review division to aid in review, such as sponsor derived Standardized Medical Dictionary for Regulatory Activities Query (MedDRA SMQ) flags and/or custom MedDRA queries for DILI.

Laboratory Analysis Data Set (ADLB): This data set contains one record per lab test, per collection, per subject data set. The laboratory tests of most interest are noted below in the full description for SDTM.LB, but this specification contains additional analysis variables to be submitted in ADLB. However, it is acceptable for additional laboratory tests to be included. If the submitted data set is greater than 5 GB, the data set should be split according to laboratory panels of hematology, chemistry, urinalysis, and other (if necessary, for miscellaneous tests). This data set is designed to be equivalent to an ADaM compliant Basic Data Structure (BDS) laboratory data set with additional review division specific variables.

Drug-Induced Liver Injury Analysis Data Set (ADDILI): This custom data set contains one record per parameter per subject, where each subject should have a minimum of one parameter to evaluate potential DILI. Subjects deemed to have potential DILI should have two additional parameters: one to list the action taken and another to list the outcome. This data set also contains variables derived from pertinent data from the ADLB data set, such as post-baseline maximum values for each of the liver enzymes. In addition, this data set contains flags to indicate any additional work-up conducted to evaluate potential DILI. Sponsors may create new variables to support the analysis or additional parameters using the existing variables (or both) in consultation with the FDA.

Microscopic Findings Analysis Data Set (ADMI): This custom data set contains one record per biopsy parameter, per evaluator, per collection, per subject. This data set is meant to capture all source biopsy records and evaluate subjects with respect to the histological endpoints as designated by the study protocol. Each histological endpoint is given its own parameter and evaluated as "Y" or "N" in AVALC. Additional criteria and analysis flags should also be included as needed from the sponsor. This data should be submitted when the histological data are collected and reported to FDA.

Non-Invasive Serum Biomarkers of Liver Fibrosis and NASH Analysis Data Set (ADRS): The ADRS data set contains the non-invasive NASH and fibrosis serum biomarkers sponsors may wish to evaluate such as Cytokeratin-18 (CK-18), MELD score, Enhanced Liver Fibrosis (ELF) score, Liver Fibrosis (FIB-4) score, Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), etc. Measurements may be derived as calculations from datapoints in other data sets such as SDTM.LB or SDTM.RS. This data set follows the same structure as the SDTM.RS domain but contains additional parameters; each non-invasive endpoint (e.g., MELD Score from Baseline <12 to >=15 post-baseline) is given its own parameter and evaluated as "Y" or "N" in AVALC. Additional criteria and analysis flags should be included as the sponsor sees fit. This data should be submitted when the non-invasive serum biomarkers are collected and reported to FDA.

Analysis Time to Event Data Set (ADTTE): This data set is one record per parameter per subject. Sponsors should use this data set to evaluate time-to-event endpoints for all treated subjects. This guidance contains sample parameters, but sponsors should consult with the FDA on the specific parameters relevant to their program.

5.0 Overview of Data Set Specifications

Each section below provides specifications and/or appropriate CDISC Controlled Terminology that describes the desired content and structure of the data set. The variable names and associated metadata are based on current CDISC SDTM and ADaM standards where possible. If any variable is unclear, sponsors are encouraged to discuss the expectations with DHN.

Sponsors are strongly encouraged to seek DHN input for additional custom data sets and variables to support determination of efficacy and/or safety. Though sponsors should consider

the data sets referenced in this guidance as the FDA's recommendation to support regulatory review, some variables may not be appropriate for all clinical trials.

CDISC Controlled Terminology developed and maintained by CDISC and National Cancer Institute Enterprise Vocabulary Services (NCI EVS)[6] should be used where applicable, but codelists may be extensible. If a submission used alternate controlled terminology or extended any codelist, then sponsors should indicate this in the define.xml document. The variable labels and the variable type noted in the specifications should be used. As updates are made to CDISC Controlled Terminology, sponsors should use the current version provided by CDISC and NCI EVS.

5.1 SDTM Domains

5.1.1 Biospecimen Events (BE) Domain

The BE domain should contain information regarding the collection of specimens that are used for histologic assessment within the Microscopic Findings (MI) domain, including the anatomic location from which the specimen was collected. The collection event is linked to the Biospecimen Findings (BS) domain that stores information regarding any measurements performed on the specimens. For example, a tissue sample that is collected, extracted, frozen, shipped, and thawed should have five records, each with a BEDECOD value of "COLLECTING", "EXTRACTING", "FREEZING", "SHIPPING" and "THAWING" respectively.

A complete listing of the variables to be included in the BE domain is located on the CDISC website (SDTMIG-PGx v1.0).[7] The NCI EVS contains a complete codelist for the terminology of the events to be captured (BEDECOD) in the BE domain.

5.1.2 Biospecimen Findings (BS) Domain

Sponsors should provide a complete listing of all characteristics of biospecimens and extracted samples used for analysis in the Microscopic Findings (MI) domain. These measurements are used to assess the adequacy and integrity of the samples collected.

A complete listing of the variables to be included in the BS domain is located on the CDISC website (SDTMIG-PGx v1.0).[8] Sponsors should collect and submit information for the following Biospecimen Characteristics Test Name (BSTEST) values:

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[6] Available at https://evs.nci.nih.gov/ftp1/CDISC/SDTM/SDTM%20Terminology.pdf.

[7] The BE domain is included in the SDTMIG-PGx v1.0. Future versions of the SDTMIG may include the BE domain (instead of in a separate SDTMIG-PGx). Available at https://www.cdisc.org/standards/foundational/pgx-sdtmig/sdtmig-pgx-v1-0-impending-deprecation.

[8] The BS domain is included in the SDTMIG-PGx v1.0. Future versions of the SDTMIG may include the BS domain (instead of in a separate SDTMIG-PGx). Available at https://www.cdisc.org/standards/foundational/pgx-sdtmig/sdtmig-pgx-v1-0-impending-deprecation.

Table 1: Biospecimen Domain Test Values

BSTESTCD	BSTEST	BSORRES	*Notes*
DIAMETER	Diameter		This test is extended from the BSTEST codelist.
LENGTH	Length		The result should be reported in millimeters (mm).
NEEDSIZE	Needle Size	e.g., 16	The unit of "NEEDLE GAUGE" would be captured under BSORRESU. This test is extended from the BSTEST codelist.

It is important to note that sponsors may submit additional tests to support the decision to include or exclude the sample from analysis. In addition, sponsors may use the Related Records (RELREC) domain to connect the specimens between the BS and MI domains.

5.1.3 Microscopic Findings (MI) Domain

Currently, the surrogate endpoints that are acceptable to DHN for a phase 3 trial to support approval for treatment of noncirrhotic NASH with fibrosis under the accelerated approval pathway (Subpart H) are biopsy-based. A semi-quantitative scoring system that considers a core set of histological features known as the NASH Clinical Research Network (CRN) Scoring System is used to assess NASH. Sponsors may provide data for additional scoring systems conforming to CDISC standards.[9]

Subjects should have an overall histological diagnosis of NASH with liver fibrosis before the NASH CRN Score applies. The NASH CRN Scoring System consists of an evaluation of fibrosis using the NASH CRN Fibrosis Stage and the NAFLD Activity Score (NAS), where NAS is a composite assessment of degrees of steatosis, lobular inflammation, and hepatocellular ballooning.[10] For drug development programs intended for treatment of noncirrhotic NASH with liver fibrosis, FDA has accepted as critical inclusion criteria in NASH trials a NAS greater than or equal to 4 with at least 1 point each in inflammation and ballooning along with a NASH CRN fibrosis score greater than stage 1 fibrosis but less than stage 4 fibrosis.

Liver biopsy data can be tabulated using CDISC's MI Domain. The MI domain is designed to hold information generated from histological, pathological, and immunohistological images obtained via microscopic evaluations of tissue samples. The MI domain provides a record for each microscopic finding observed, where multiple microscopic tests on a specimen may be conducted.

As the biopsy tissue may be processed into multiple slides prior to histopathological evaluation, each individual slide may be assessed for individual NASH components. Sponsors should

[9] Available at https://www.cdisc.org/standards.

[10] DE Kleiner, EM Brunt, M VanNata, et al., 2005, Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease, Hepatology, 41(6):1313-1321.

determine whether or not the individual slides are adequate for assessment and record those results in the Supplemental MI (SUPPMI) domain. Sponsors should also link records within the MI, BS, and BE domains via a RELREC domain. Based on the specifications of the MI domain and the CDISC Controlled Terminology approved thus far for liver fibrosis scoring, each specific component of the NAS should be recorded using the Microscopic Findings Test Detail (MITSTDTL) variable. Likewise, the total or composite NAS score is represented with MITSTDTL of "Total Score" with the criteria (NAS) being held in Microscopic Findings Test Code (MITESTCD) and Microscopic Findings Test (MITEST) variables, to group the individual components and composite score of NAS.

Given that histological assessments of NAFL and NASH are subject to inter- and intra-observer variability,[11] sponsors should capture the observer details in the MI domain using the Evaluator (MIEVAL) and Evaluator ID (MIEVALID) variables. The measure evaluator is stored in MIEVAL, and within the MIEVALID variable when distinction between multiple evaluators with the same role is necessary. Where MIEVALID is populated, MIEVAL should exist and have a non-null value. CDISC Controlled Terminology should be used to populate the values for these variables. In cases where multiple evaluators provide assessments for a given time point measurement or for an overall assessment, an independent assessor identifies one of multiple measurements to be the accepted one and should be indicated through use of the Accepted Record Flag variable (MIACPTFL). Values for this variable are not meant to be derived by the sponsor.

CDISC Controlled Terminology provides values of "Fibrosis" within MITESTCD and MITEST. While there is currently no specified terminology published by CDISC for the NASH CRN Fibrosis Stage, CDISC does provide terminology for other liver fibrosis scoring criteria for use with the Microscopic Findings Test Detail (MITSTDTL) variable. MITSTDTL is a qualifier variable for MITESTCD and MITEST. Based on this, it is recommended to specify NASH CRN Fibrosis Stage in MITSTDTL, used in conjunction with MITESTCD and MITEST of "Fibrosis." Results from the biopsy can be specified using the Microscopic Findings Original Result (MIORRES) variable.

A list of the relevant variables to be included in the MI domain is available in the SDTM Implementation Guide.[12] Tables 2 (recommended) and 3 (permissible) below contain a representation of concepts for the MI domain. Sponsors should discuss with the review division if any of the permissible tests are required for an individual trial. Sponsors should store any comments about the biopsy or slide readings in a Comments (CO) domain.

[11] DE Kleiner, HR Makhlouf, 2016, Histology of NAFLD and NASH in Adults and Children, Clin Liver Dis, 20(2):293–312.

[12] Available at https://www.cdisc.org/standards/foundational/sdtmig/sdtmig-v3-3.

Table 2. Recommended Microscopic Findings Test Codes, Tests, Test Details and Results[13]

MITESTCD	MITEST	MITSTDTL	MIORRES
NASHIND	Histological Presence of NASH with Fibrosis Indicator		Yes, No
NAS	NAFLD Activity Score	STEATOSIS	0, 1, 2, 3
NAS	NAFLD Activity Score	LOBULAR INFLAMMATION	0, 1, 2, 3
NAS	NAFLD Activity Score	BALLOONING	0, 1, 2
NAS	NAFLD Activity Score	TOTAL SCORE	0, 1, 2, 3, 4, 5, 6, 7, 8
STEAT	Steatosis	STEATOSIS GRADE	<5%, 5-33%, >33-66%, >66%
STEAT	Steatosis	STEATOSIS LOCATION	Zone 3, Zone 1, Azonal, Panacinar
STEAT	Steatosis	MICROVESICULAR STEATOSIS	Present, Absent
FIBROSIS	Fibrosis	NASH CRN FIBROSIS STAGE	None, Mild zone3, Moderate zone 3, Portal/periportal, Zone 3 & Periportal, Bridging, Cirrhosis
INFLAM	Inflammation	LOBULAR INFLAMMATION	No foci, <2 foci, 2-4 foci, >4 foci
INFLAM	Inflammation	PORTAL INFLAMMATION[14]	None to minimal, >Minimal
HCCINJ	Hepatocellular Injury	BALLOONING DEGENERATION	None, Few, Many
PTNUM	Number of Portal Tracts		

Table 3. Permissible Microscopic Findings Test Codes, Tests, Test Details and Results

MITESTCD	MITEST	MITSTDTL	MIORRES
FIBROSIS	Fibrosis	ISHAK FIBROSIS SCORE	0-18
INFLAM	Inflammation	MICROGRANULOMAS	Present, Absent

[13] Note: The terminology listed in the table below is proposed terminology.

[14] Portal Inflammation is recommended for pediatric trials and permissible for adult trials.

MITESTCD	MITEST	MITSTDTL	MIORRES
HCCINJ	Hepatocellular Injury	ACIDOPHIL BODIES	None to rare, Many
HCCINJ	Hepatocellular Injury	MALLORY BODIES	None to rare, Many
HCCINJ	Hepatocellular Injury	PIGMENTEED MACROPHAGES	None to rare, Many
HCCINJ	Hepatocellular Injury	MEGAMITOCHONDRIA	None to rare, Many

5.1.4 Supplemental Microscopic Findings (SUPPMI) Domain

Sponsors should provide a Supplemental Microscopic Findings (SUPPMI) domain with a parameter to assess the adequacy of biopsy sample(s) collected for analysis. Adequacy of the slide(s) created for evaluating the histopathological features (e.g., ballooning, steatosis) should be established based on results collected in the BS and MI domains. Sponsors should provide their rationale in the supplemental qualifier "Image Condition" for slides determined to be not adequate for analysis. If there are multiple reasons, "Image Condition" should take a value of "MULTIPLE" with the individual reasons listed in QVAL for "Image Condition 1" and "Image Condition 2". Sponsors may provide additional slide-level data points in the SUPPMI domain as they see fit (e.g., evaluator name, container name). The table below provides the variables and terminology to be used for assessing adequacy of the sample.

Table 4. Terminology for SUPPMI Domain

RDOMAIN	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
MI	*Use these variables to link back to MI domain*		MIOIQ	Overall Image Quality	Expected Values: Adequate, Not Adequate
MI			MIIMCND	Image Condition	e.g., Blurry Image, Cracked Slide, Multiple
MI			MIIMCND1	Image Condition 1	*List Condition 1 if Multiple Conditions*
MI			MIIMCND2	Image Condition 2	*List Condition 2 if Multiple Conditions*

5.1.5 Disease Response and Clinical Classifications (RS) Domain

CDISC provides specific guidance for characterizing and recording clinical indicators of hepatic disease progression including MELD Scoring,[15] West Haven Hepatic Encephalopathy Grade,[16] and Child-Pugh Classification[17] in the RS domain.

- **MELD and MELD Sodium (MELD-Na):** While there are no current CDISC guidance for MELD-Na, sponsors should follow a similar modeling strategy as MELD scoring as shown in Table 5. Individual laboratory test result values (e.g., Creatinine, Bilirubin, INR) should be represented in the LB domain and composite scoring in the RS domain where the linkage is represented using the --LNKID variable. The relationship between the two domains is stored in the RELREC domain.

- **West Haven Hepatic Encephalopathy Grade**: The measure evaluator is stored in Evaluator (RSEVAL), and if distinction between multiple evaluators with the same role is necessary this information is stored within the Evaluator ID (RSEVALID) variable. Where RSEVALID is populated, RSEVAL should exist and have a non-null value. Results should be populated in the Original (RSORRES) and Standard Character (RSSTRESC) Results variables, and take values of "GRADE 0", "GRADE 1", "GRADE 2", "GRADE 3", or "GRADE 4".

- **Child-Pugh Classification**: Guidance provided by CDISC provides a way to represent the individual laboratory test result values in the LB domain collection of ascites information in the CE domain, and composite scoring in the RS domain where the linkage is represented using the --LNKID variable from each of the domains. For example, a serum bilirubin result of 2.3 mg/dL would result in a RSORRES of "2 to 3" and a RSSTRESN value of 2 where RSTEST = "CPS01-Serum Bilirubin." The relationship between the two domains is represented in a RELREC domain. Since the input to the Child-Pugh Encephalopathy Grade parameter originates from the West Haven Hepatic Encephalopathy Grade that is also modeled in the RS domain (see above section on "West Haven Hepatic Encephalopathy Grade"), the guidance further provides linking of these two RS records through the use of the RSGRPID variable.

The table below provides CDISC Controlled Terminology that has been developed for RSCAT, RSTESTCD and RSTEST. Refer to the current version of the NCI EVS to ensure no changes to the terminology relevant to the RS domain.

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[15] Available at https://www.cdisc.org/standards/foundational/qrs/model-end-stage-liver-disease.

[16] Available on the https://www.cdisc.org/ website after login at https://www.cdisc.org/system/files/members/standard/foundational/qrs/SDTM%20RS-WH%20Hepatic%20Encephalopathy%20Grade%20v1%20Public%20Domain.pdf.

[17] Available on the https://www.cdisc.org/ website after login at https://www.cdisc.org/system/files/members/standard/foundational/qrs/SDTM%20RS-Child-Pugh%20v1%20Public%20Domain.pdf.

Table 5. CDISC Controlled Terminology Disease Response and Clinical Classifications (RS) Domain[18]

RSCAT	RSTESTCD	RSTEST	CDISC Definition (taken from CDISC Controlled Terminology)
MELD	MELD0101	MELD-01 Score	Model for End Stage Liver Disease–MELD Score.
MELD-NA	MELD0201	MELD-02 Score	Model for End Stage Liver Disease-Sodium – MELD-Na Score.
WEST HAVEN HEPATIC ENCEPHALOPATHY GRADE	WHEG0101	WHEG01-WH Hepatic Encephalopathy Grade	West Haven Hepatic Encephalopathy Grade – Grade.
CHILD-PUGH CLASSIFICATION	CPS0101	CPS01-Encephalopathy Grade	Child-Pugh Classification - Encephalopathy Grade.
	CPS0102	CPS01-Ascites	Child-Pugh Classification - Ascites.
	CPS0103	CPS01-Grade	Child-Pugh Classification - Child-Pugh grade.
	CPS0104	CPS01-PT, INR	Child-Pugh Classification - Prothrombin time, international normalized ratio (INR).
	CPS0105A	CPS01-PT, Sec Prolonged	Child-Pugh Classification - Prothrombin time, sec prolonged.
	CPS0105B	CPS01-Serum Albumin	Child-Pugh Classification - Serum albumin, g/dL.
	CPS0106	CPS01-Serum Bilirubin	Child-Pugh Classification - Serum bilirubin, mg/dL.
	CPS0107	CPS01-Total Score	Child-Pugh Classification - Child-Pugh total score.

5.1.6 Imaging Results (ZI) Domain[19]

The custom ZI domain captures results of liver imaging procedures (e.g., MRI or CT scan).

[18] Note: MELD-NA terminology is proposed terminology and not listed in the NCI EVS.

[19] Note: Future releases of the SDTMIG may contain a Gastrointestinal System Findings (GI) domain as discussed in the Crohn's Disease Therapeutic Area User Guide (TAUG). If and when the GI domain becomes available in a future version of the SDTMIG and if the FDA supports that new version, sponsors may choose to submit ZI findings into the GI domain.

Sponsors may choose to conduct imaging procedures to further investigate the liver during the clinical trial, including measurements for liver steatosis, inflammation, and/or fibrosis. Imaging-based biomarkers are currently not accepted by DHN to support primary efficacy assessments in trials intending to support a marking application; however, they can be used to assess efficacy in early phase trials and as exploratory or secondary endpoints to provide supportive evidence. It is therefore important for these data points to be submitted consistently. The procedure itself should be recorded in the Procedures (PR) domain and results of the procedure should be recorded in this custom Imaging Results (ZI) domain. Information on the device(s) used to capture images from MRIs and other imaging-related data should be captured in domains as prescribed by the SDTMIG for Medical Devices (SDTMIG-MD).[20]

The ZI domain takes the structure of a findings domain and should contain variables such as Imaging Results Test (ZITEST), Imaging Results Test Code (ZITESTCD), and Imaging Results Original Result (ZIORRES). Sponsors may use their discretion regarding which data points to collect and submit from the imaging procedure(s). Recording of the procedure in the PR domain and results of that procedure in the ZI domain may be linked via the RELREC domain.

5.1.7 Adjudication (ZA) Domain

Sponsor protocols may specify for certain events and/or clinical outcomes to be adjudicated by investigator(s) and/or committee(s). Sponsors should create a custom Adjudication (ZA) domain to provide assessments by individual adjudicators as it relates to certain events (e.g., DILI). Examples of adjudicated events in NASH development programs may include DILI, Liver-Related Death, Hepatic Decompensation Events, Major Adverse Cardiac Events (MACE) and Cardiac-Related Death. All potential events sent for adjudication should be included in the data set regardless of the adjudication outcome.

The ZA domain should follow the structure of a Findings About Events or Interventions (FA) domain. An FA domain utilizes the SDTM findings class structure with the addition of an "Object" (--OBJ) variable that serves to specialize the topic being measured within the --TESTCD/--TEST variable.

Sponsors should specify in their protocol and in the ZA domain the event that is being adjudicated, type of investigator assessing the event as well as the committee responsible for resolving any discrepancies between individual adjudicators. For example, the custom ZA Domain may provide DILI assessments and/or Liver-Related Death/Clinical Outcomes by individual hepatologists and a Hepatic Adjudication Committee (HAC), if applicable. MACE and Cardiac-Related Death events may be adjudicated by a Cardiac Adjudication Committee (CAC).

The date of the adjudicator's assessment may be stored in ZADTC. The earliest date that the assessor determines the subject to have met the criteria should be modeled as its own record with ZATEST value of "EVALUATED EVENT ONSET DATE" with the date value stored in ZAORRES. The Object (ZAOBJ) variable should hold the name of the event being evaluated, such as "DILI" or "CARDIAC MACE." Each block of records resulting from the assessment of

[20] Available at https://www.cdisc.org/standards/foundational/medical-devices-sdtmig/sdtmig-medical-devices-v1-1.

a single adjudicator per adjudication event should be grouped using a unique Repetition Number (ZAREPNUM) variable. The Category (ZACAT) variable may be used to distinguish if the adjudication is a 'FIRST ADJUDICATION' or a 'READJUDICATION.'

For assessing potential DILI, each adjudicator's assessment should include a category of likelihood that the investigational or study product caused DILI. We recommend the likelihood categories used by the Drug-Induced Liver Injury Network's[21] numeric score of 1 to 6 (1 = Definite, 2 = Highly Likely, 3 = Probable, 4 = Possible, 5 = Unlikely, or 6 = Indeterminate). If a HAC was used, then consensus assignment of likelihood category should also be provided (and noted in the ZAEVAL variable). If the adjudicator is reviewing lab data to determine whether the subject meets potential DILI injury, the records from the LB domain and the record(s) in the ZA domain may be linked using the RELREC domain.

For assessing whether a subject meets given criteria (e.g., cardiac-related death), sponsors should include in their study protocol the specific criteria being used for the event being adjudicated. The Test (ZATEST) variable may take a value such as "EVENT CRITERIA MET" with the event itself stored in the ZAOBJ variable. The result variable (ZAORRES) may take values of "Yes" or "No." Any comments made by an adjudicator or an adjudication committee the sponsor wishes to submit should be stored in the Comments (CO) domain, linked to the ZA domain via the RELREC domain.

For assessing hepatic decompensation events requiring adjudication, the ZAOBJ variable could take a value of "HEPATIC DECOMPENSATION EVENT." The adjudicator's assessment of the specific event causing the subject to reach the endpoint is stored in ZAORRES where ZATEST = "ADJUDICATION OUTCOME" with the adjudicator's assessment of when the subject reached that endpoint stored in ZAORRES where ZATEST = "EVALUATED EVENT ONSET DATE."

Table 6 contains the variables and subsequent comments, and Table 7 contains example terminology for adjudicated events and outcomes.

Table 6. ZA Variables

Variable Name	Variable Label	Type	Comments
Adjudication Test and Results			
ZATESTCD	Adjudication Test Code	Char	*See Table 7.*
ZATEST	Adjudication Test	Char	*See Table 7.* Sponsors may include additional tests beyond what is listed in Table 7. Additional tests can apply to all objects or some objects (i.e. sponsors are permitted to submit an object-specific test).
ZAOBJ	Object of Interest	Char	*See Table 7.* The category of event that is being adjudicated, e.g., 'DILI', 'CARDIAC MACE'.

[21] Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3637941/pdf/nihms-444700.pdf.

Variable Name	Variable Label	Type	Comments
			If the trial protocol calls for additional events or outcomes to be adjudicated, sponsors may extend the codelist beyond what is listed in Table 7.
ZACAT	Category	Char	Used to define if the adjudication is a first adjudication or re-adjudication.
ZAORRES	Original Result	Char	The adjudicator's assessment of ZATEST.
ZASTRESC	Standard Character Result	Char	Standardized Result of the adjudicator's assessment of ZATEST.
Adjudicator Information			
ZAEVAL	Evaluator	Char	Role of the person who provided the evaluation. Used only for results that are subjective (e.g., assigned by a person or a group). Should be null for records that contain collected or derived data. Examples: INVESTIGATOR, ADJUDICATION COMMITTEE, VENDOR.
ZAEVALID	Evaluator Identifier	Char	Used to distinguish multiple evaluators with the same role recorded in ZAEVAL. Examples: "Hepatologist 1", "Hepatologist 2". ZAEVAL should be populated when ZAEVALID is populated.
Other Flags			
ZAACPTFL	Accepted Record Flag	Char	The Acceptance Flag identifies those records that have been determined to be the accepted assessment by an independent assessor. This flag would be provided by an independent assessor and when multiple evaluators (e.g., "Hepatologist 1", "Hepatologist 2", and "Hepatic Adjudication Committee") provide assessment or evaluations at the same time point or an overall evaluation.

Table 7. Example Terminology for Adjudicated Events and Outcomes

ZAOBJ	ZATESTCD	ZATEST	ZAORRES
DILI	ADJDILI	DILI ADJUDICATION SCORE	1-6
	ADJDATE	EVALUATED EVENT ONSET DATE	*Adjudicator's assessment of when the subject met event criteria*
CARDIAC MACE	ADJCRIT	EVENT CRITERIA MET	Yes, No
	ADJDATE	EVALUATED EVENT ONSET DATE	*Adjudicator's assessment of when the subject met event criteria*
CARDIAC DEATH	ADJCRIT	EVENT CRITERIA MET	Yes, No
	ADJDATE	EVALUATED EVENT ONSET DATE	*Date of Death*
	ADJCRIT	EVENT CRITERIA MET	Yes, No

ZAOBJ	ZATESTCD	ZATEST	ZAORRES
LIVER-RELATED DEATH	ADJDATE	EVALUATED EVENT ONSET DATE	*Date of Death*
CAUSE OF DEATH	ADJOUT	ADJUDICATION OUTCOME	*Adjudicator's assessment of cause of death*
	ADJDATE	EVALUATED EVENT ONSET DATE	*Date of Death*
HEPATIC DECOMPENSATION EVENT	ADJOUT	ADJUDICATION OUTCOME	HEPATIC ENCEPHALOPATHY, ASCITES, VARICEAL BLEED, SPONTANEOUS BACTERIAL PERITONITIS
	ADJDATE	EVALUATED EVENT ONSET DATE	*Adjudicator's assessment of when the subject met event criteria*

5.1.8 Concomitant Medications (CM) Domain

Sponsors should provide a complete list of all Concomitant Medications data for all subjects in accordance with existing CDISC standards. In addition to prescription medications, sponsors should include any over the counter medications (e.g., weight loss medication, dietary and herbal medications). Of particular interest are lipid-lowering agents, statins, antihypertensive, antidiabetic, thiazolidinediones, vitamin E, and anticoagulants and antiplatelets. Data relating to concomitant medications should be captured and recorded during scheduled visits as reflected in the trial protocol and when the subject is undergoing evaluation for potential DILI.

5.1.9 Medical History (MH) Domain

Sponsors should provide a complete listing of all Medical History data for all subjects in accordance with existing CDISC standards. Of particular interest are preexisting medical conditions that may impact NASH disease progression and/or DILI assessment (e.g., diabetes, primary liver cancers, alcohol/substance use disorder, gallstone disease, heart failure, etc.). Sponsors should refer to the draft NASH Guidance regarding recommendations for trial enrollment depending on the phase of drug development. Additionally, sponsors should include a record in the MH domain for any condition that precludes a subject from participating in the study, in addition to their record in the Inclusion/Exclusion (IE) domain.

5.1.10 Laboratory (LB) Domain

Sponsors should provide the complete tabulated data for all lab measurements recorded, including central and local labs (denoted using LBNAM variable) as well as scheduled and unscheduled visits. All lab data should be provided in accordance with CDISC Standards and Controlled Terminology. Sponsors should discuss specific laboratory parameters to be collected with DHN. Recommended parameters are listed below:

- Hematology parameters (e.g., white blood cell, hemoglobin, platelets)
- Metabolic parameters (e.g., electrolytes, hemoglobin A1C, creatine kinase, lactate dehydrogenase)
- Liver parameters including bilirubin fractions[22] (e.g., direct and indirect or conjugated and unconjugated)
- Renal parameters (e.g., creatinine, estimated glomerular filtration rate)
- Lipid parameters
- Coagulation parameters (e.g., prothrombin time/international normalized ratio)
- Autoimmune parameters (e.g., Antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), Total IgG levels)

In addition to the above tests, sponsors may wish to include other serum biomarkers that may be relevant to understanding NASH, fibrosis, and/or DILI (e.g., ELF,[23] CK-18, APRI, FIB-4, N-terminal propeptide of type III collagen (PRO-C3)). Note that individual components of calculated serum biomarkers should have their own record(s) in the LB domain. Any biomarker that is derived from individual components should store the analytical method used for calculation stored in the Analysis Method variable (LB.LBANMETH). Terminology for the components of and results for the afore mentioned example serum biomarkers are provided below in Table 8. All lab parameters submitted to FDA should follow CDISC Controlled Terminology.

Table 8. CDISC Controlled Terminology for Example Liver Serum Biomarkers in LB Domain[24]

LBTESTCD	LBTEST	NCI Code	CDISC Definition
ELF Components			
TIMP1	Tissue Inhibitor of Metalloproteinase 1	C82036	A measurement of the tissue inhibitor of metalloproteinase 1 in a biological specimen.
P1NP	Procollagen 1 N-Terminal Propeptide	C96625	A measurement of the procollagen 1 N-terminal propeptide in a biological specimen.
HYALUAC	Hyaluronic Acid	C112319	A measurement of hyaluronic acid in a biological specimen.

[22] Sponsors should use appropriate terminology to clearly reflect the method used to assess bilirubin fractions (i.e., *conjugated* vs. *direct*).

[23] If the ELF Score is calculated histologically, the result should be stored in the MI domain for MI.MIORRES under MI.MITSTDTL = "ENHANCED LIVER FIBROSIS SCORE" and MI.MITESTCD = 'FIBROSIS'.

[24] The line item for Enhanced Liver Fibrosis is proposed terminology in the LB domain as a calculation from the individual components (TIMP1, P1NP, HYALUAC).

LBTESTCD	LBTEST	NCI Code	CDISC Definition
Example Liver Serum Biomarkers			
ELF	Enhanced Liver Fibrosis		
APRI	AST to Platelet Ratio Index	C156512	A calculation that indicates the likely presence of liver cirrhosis and fibrosis, measured as the relative measurement of aspartate aminotransferase (AST) to AST upper limit of normal, divided by the platelet count, and multiplied by 100.
CYFRA18	Cytokeratin 18 Fragment	C130160	A measurement of the cytokeratin 18 fragment in a biological specimen.
LVFBRSC	Liver Fibrosis Score	C147385	A scoring system that evaluates liver pathology through the assessment of multiple blood test parameters, taking into account additional demographic factors such as the age and/or gender of the subject.
P3NP	Procollagen 3 N-Terminal Propeptide	C128973	A measurement of the procollagen 3 N-terminal propeptide in a biological specimen.

5.1.11 Microbiology Specimens (MB) Domain

Sponsors should use the MB domain to provide serologic test results for hepatitis (hepatitis A, B, C, and E) serology tests collected as part of the trial entry evaluation and during potential DILI assessments, if applicable. CDISC Controlled Terminology for the hepatitis tests are provided below:

Table 9. CDISC Controlled Terminology for Hepatitis Serology in Microbiology Specimens Domain

MBTESTCD	MBTEST	NCI Code	CDISC Definition
HAAB	Hepatitis A Virus Antibody	C92534	A measurement of the hepatitis A virus antibody in a biological specimen.
HAIGMAB	Hepatitis A Virus IgM Antibody	C92271	A measurement of hepatitis A virus IgM antibody in a biological specimen.
HBSAG	Hepatitis B Virus Surface Antigen	C64850	A measurement of the surface antigen reaction of a biological specimen to the hepatitis B virus.
HBCAB	Hepatitis B Virus Core IgM Antibody	C96660	A measurement of the hepatitis B virus core antibody in a biological specimen.
HCAB	Hepatitis C Virus Antibody	C92535	A measurement of the hepatitis C virus antibody in a biological specimen.
HCRNA	Hepatitis C Virus RNA	C142330	A measurement of the hepatitis C virus RNA in a biological specimen.
HEIGGAB	Hepatitis E Virus IgG Antibody	C106526	A measurement of IgG antibody to the hepatitis E virus in a biological specimen.
HEIGMAB	Hepatitis E Virus IgM Antibody	C96665	A measurement of IgM antibody to the hepatitis E virus in a biological specimen.
HERNA	Hepatitis E Virus RNA	C142331	A measurement of the hepatitis E virus RNA in a biological specimen.

5.1.12 Substance Use (SU) Domain

Data related to substance use (e.g., alcohol use) should be collected as part of the NASH clinical trial and DILI evaluation. The extent of prior alcohol use should be assessed at baseline, during protocol-defined scheduled visits, and in suspected cases of DILI. Data collected should be recorded in the SU domain and included in the Inclusion/Exclusion (IE) domain as appropriate. Other substances such as tobacco or caffeine usage should also be recorded in the SU domain. For example, a subject who consumes one, regular-sized beer per day may contain the following data points:

- SUTRT: BEER
- SUCAT: ALCOHOL
- SUDOSE: 12
- SUDOSU: OUNCES
- SUDOSFRQ: QD

The full list of variables to be included in the SU domain is located in the SDTM Implementation Guide.

5.1.13 Trial Summary (TS) Domain

Data related to the trial summary should be collected and stored in the Trial Summary (TS) domain. Of particular interest to FDA is the frequency that this technical specification is used in creating and submitted trial data. Per the FDA *Study Data Technical Conformance Guide*, sponsors may include an additional parameter in their TS domain to note that this technical specification was used for the study. The parameter and associated value sponsors should use is noted below:

- TSPARAMCD = FDATCHSP
- TSPARAM = FDA Tech Spec
- TSVAL = NASH Technical Specification Guidance v1.0

5.1.14 RELREC Domain

As discussed in previous sections, sponsors should use a RELREC domain to describe the relationship between records captured in separate domains together. A common use case for the RELREC domain is connecting AE and CM records. As it relates to this technical specification, the RELREC domain may connect the needle size captured in the BS domain with the biopsy slide measurements evaluated in the MI domain. Another example may be connecting the record of an MRI procedure in the PR domain with the results of that MRI in the ZI domain. Where relationships between records in different domains should be established, the RELREC domain should store those relationships.

The full instructions for creating the RELREC domain, including the required variables, are located in the SDTM Implementation Guide.

5.1.15 Other SDTM Considerations

5.1.15.1 Gastroesophageal varices

Subjects who progress to cirrhosis during the trial may undergo screening for gastroesophageal varices on esophagogastroduodenoscopy (EGD). Information on the EGD can be modeled in SDTM using the Procedures Domain (PR). The PR domain falls within the Interventions Class of domains and is intended to capture information on interventional activity that are to have diagnostic, preventive, therapeutic, or palliative effects. The name of the procedure, EGD, can be captured Reported Name of Procedure (PR.PRTRT).

Currently, CDISC does not have any guidance on modeling the results of the EGD procedure related to varices (e.g., number of varices, size of varices, presence of red wale marks). Given that CDISC has a draft domain for Gastrointestinal System Findings (GI) that may be under development, the current recommendation is to model the results of the EGD procedure in the custom Imaging Results (ZI) domain that follows the structure of a CDISC findings domain. Occurrence of varices, red wale marks, and variceal bleeding can be modeled under using ZITESTCD and ZITEST Test Codes and Test Names. Sponsors may submit additional data points about the results of the endoscopy in the ZI domain.

When gastroesophageal variceal hemorrhage is captured as an AE, it should be captured in the AE domain, with verbatim term indicating gastroesophageal variceal hemorrhage captured in the topic variable of AE.AETERM. The record in the AE domain should be linked to that of the ZI domain using the --LNKID variable, with relationships captured using the RELREC domain.

5.1.15.2 All-cause mortality

All-cause mortality or death is a component of several composite endpoints currently accepted by DHN to demonstrate clinical benefit in NASH clinical trials. If a subject dies during the study, information regarding the subject's death is tabulated in several SDTM domains including the Death Details (DD) domain, which should store all death information regardless of whether the death is related to the primary endpoint. Additional domains which should include death information are the Disposition (DS) domain that records the death as a disposition event, Adverse Events (AE), and Demographics (DM) to populate the Death Date (DTHDTC), and Death Flag (DTHFL) variables that are referenced within this domain. The records within the AE, DS, and DD domains should be linked using the --LNKID variable, with the relationship represented in the RELREC domain. Sponsors should consult CDISC Controlled Terminology as well as the SDTM Implementation Guide in using these domains.

5.2 ADaM Data Sets

This section contains three parts: Analysis Data Set Subject Level (ADSL), Occurrence Data Structure (OCCDS) data sets, and Basic Data Structure (BDS) data sets. At a minimum, sponsors should provide the data sets and variables listed throughout these sections. Sponsors can and

should submit additional data sets and variables beyond what is listed below in accordance with the ADaM Implementation Guide (ADaMIG)[25] and the FDA Data Standards Catalog.

Sponsors should also include appropriate Sequence Number variables in their ADaM data sets for easy traceability back to the SDTM domains. Specific instructions are located in the ADaM Implementation Guide.

5.2.1 Subject-Level Analysis Data Set (ADSL)

The Subject-Level Analysis Data Set contains one record per subject and derives information from other data sets for analysis purposes. Sponsors should include all required variables in the ADSL, including basic demographic information, treatment variables, start and end date variables, study and treatment discontinuation variables, and treatment duration variables. The variables listed in Table 10 should also be included in the ADSL data set to allow FDA to conduct sub-group analyses.

The baseline variables identified below should be used when those tests are collected and provided in the data submission. For example, if ELF score is not collected and reported, the ELFBL variable is not required for this data set. Sponsors may add additional flags to this data set as appropriate (e.g., special subject populations of interest for subgroup analyses or relevant concomitant medications).

Table 10 provides a list of variables that should be included in the ADSL data set. The comments column contains recommended derivations for the baseline variables. Sponsors should include their derivations in the ADaM define.xml file.

Table 10. ADSL Variables

Variable Name	Variable Label	Type	Comments
Baseline Vital Signs Characteristics Variables			
WEIGHTBL	Weight at Baseline (kg)	Num	VS.VSSTRESN where VSTEST = “WEIGHT” and VSBLFL = “Y”
HEIGHTBL	Height at Baseline (cm)	Num	VS.VSSTRESN where VSTEST = “HEIGHT” and VSBLFL = “Y”
BMIBL	Body Mass Index at Baseline (kg/m2)	Num	VS.VSSTRESN where VSTEST = “BMI” and VSBLFL = “Y”
SYSBL	Systolic Blood Pressure at Baseline (mmHg)	Num	VS.VSSTRESN where VSTEST = “Systolic Blood Pressure” and VSBLFL = “Y”
DIABL	Diastolic Blood Pressure at Baseline (mmHg)	Num	VS.VSSTRESN where VSTEST = “Diastolic Blood Pressure” and VSBLFL = “Y”
HRBL	Heart Rate at Baseline (beats/min)	Num	VS.VSSTRESN where VSTEST = “Heart Rate” and VSBLFL = “Y”

[25] Available https://www.cdisc.org/standards/foundational/adam/adamig-v1-1-release-package.

Variable Name	Variable Label	Type	Comments
RESPBL	Respiratory Rate at Baseline (breaths/min)	Num	VS.VSSTRESN where VSTEST = “Respiratory Rate” and VSBLFL = “Y”
WHBL	Waist to Hip Ratio at Baseline	Num	VS.VSSTRESN where VSTEST = “Waist to Hip Ratio” and VSBLFL = “Y”
Baseline Lab Characteristics			
ALTBL	Baseline ALT	Num	ADLB.AVAL where ADLB.PARAMCD = ‘ALT’ and ADLB.DILIBLFL = ‘Y’
ALTCAT	Baseline ALT Category	Text	Divide ADSL.ALTBL by LB.LBSTNRHI for the last pre-treatment record for ALT and set the category to one of the following: • If result is <=1: <= ULN • If result is >1 to <=3: > ULN to <=3x ULN • If result is >3 to <=5: >3x ULN to <=5x ULN • If result is >5: >5x ULN
ALTCATN	Baseline ALT Category (N)	Integer	Numeric Representation of ALTCAT. “1” = “<=ULN”, “2” = “>ULN to <=3x ULN”, “3” = “>3x ULN to <=5x ULN”, “4” = “>5x ULN”
ASTBL	Baseline AST	Num	ADLB.AVAL where ADLB.PARAMCD = ‘AST’ and ADLB.DILIBLFL = ‘Y’
ASTCAT	Baseline AST Category	Text	Divide ADSL.ASTBL by LB.LBSTNRHI for the last pre-treatment record for AST and set the category to one of the following: • If result is <=1: <= ULN • If result is >1 to <=3: >ULN to <=3x ULN • If result is >3 to <=5: >3x ULN to <=5x ULN • If result is >5: >5x ULN
ASTCATN	Baseline AST Category (N)	Integer	Numeric Representation of ASTCAT. "1" = "<=ULN", "2" = ">ULN to <=3x ULN", "3" = ">3x ULN to <=5x ULN", “4” = “>5x ULN”
ALPBL	Baseline ALP	Num	ADLB.AVAL where ADLB.PARAMCD = ‘ALP’ and ADLB.DILIBLFL = ‘Y’
ALPCAT	Baseline ALP Category	Text	Divide ADSL.ALPBL by LB.LBSTNRHI for the last pre-treatment record for ALP and set the category to one of the following: • If result is <=1: <= ULN • If result is >1 to <=2: > ULN to <=2x ULN • If result is >2: >2x ULN
ALPCATN	Baseline ALP Category (N)	Integer	Numeric Representation of ALPCAT. “1” = “<=ULN”, “2” = “>ULN to <=2x ULN”, “3” = “>2x ULN”
TBILIBL	Baseline Total Bilirubin	Num	ADLB.AVAL where ADLB.PARAMCD = ‘BILI’ and ADLB.DILIBLFL = ‘Y’
TBILCAT	Baseline Tot. Bilirubin Category	Text	Set to “<=ULN” if ADSL.TBILIBL <= LBSTNRHI (for the last pre-treatment record in SDTM.LB where LBTESTCD = “BILI”); else set to “>ULN” if ADSL.TBILIBL > LBSTNRHI

Variable Name	Variable Label	Type	Comments
TBILCATN	Baseline Tot. Bilirubin Category (N)	Integer	Numeric representation of ADSL.TBILCAT. "1" = "<=ULN", "2" = ">ULN"
CBILIBL	Baseline Conjugated Bilirubin	Num	ADLB.AVAL where ADLB.PARAMCD = 'BILIDIR' and ADLB.DILIBLFL = 'Y'
CBILCAT	Baseline Conj. Bilirubin Category	Text	Set to "<=ULN" if ADSL.CBILIBL <= LBSTNRHI (for the last pre-treatment record in SDTM.LB where LBTESTCD = "BILDIR"); else set to ">ULN" if ADSL.CBILIBL > LBSTNRHI
CBILCATN	Baseline Conj. Bilirubin Category (N)	Integer	Numeric representation of ADSL.CBILCAT. "1" = "<=ULN", "2" = ">ULN"
CPKCAT	Baseline CPK Category	Text	Set to "Normal" if LB.LBSTRESN <= LB.LBSTNRHI for LB.LBTESTCD = "CPK" and LB.LBBLFL = "Y"; Set to "HIGH" if LB.LBSTRESN > LB.LBSTNRHI for LB.LBTESTCD = "CPK" and LB.LBBLFL = "Y"
LDHCAT	Baseline LDH Category	Text	Set to "Normal" if LB.LBSTRESN <= LB.LBSTNRHI for LB.LBTESTCD = "LDH" and LB.LBBLFL = "Y"; Set to "HIGH" if LB.LBSTRESN > LB.LBSTNRHI for LB.LBTESTCD = "LDH" and LB.LBBLFL = "Y"
PLATCAT	Baseline Platelets Category	Text	Set to "Normal" if LB.LBSTRESN >= LB.LBSTNRLO for LB.LBTESTCD = "PLAT" and LB.LBBLFL = "Y"; Set to "LOW" if LB.LBSTRESN < LB.LBSTNRLO for LB.LBTESTCD = "PLAT" and LB.LBBLFL = "Y"
EGFRBL	Baseline eGFR	Num	Baseline eGFR value
EGFRCAT	Baseline eGFR Category	Text	Set to "Normal" if Baseline eGFR >= 90, "Mild Renal Impairment" if 60 =< Baseline eGFR < 90, "Moderate Renal Impairment" if 30 =< Baseline eGFR < 60 and "Severe Renal Impairment" if 30 > Baseline eGFR
EGFRCATN	Baseline eGFR Category (N)	Integer	Numeric representation of ADSL.EGFRCAT. "1" if "Normal", "2" if "Mild Renal Impairment", "3" if "Moderate Renal Impairment", "4" if "Severe Renal Impairment"
Baseline Medical History Characteristics			
CHRONFL	Chronic Liver Disease Flag	Char	Expected Values: "Y" or "N" Subjects with evidence of other causes of chronic liver disease at baseline should be flagged as "Y". Else, "N"
DIABFL	Diabetes Flag	Char	Expected values: "Y" or "N" "Y" if the subject is diabetic at baseline. Else, "N".
GALLFL	Gallstones Flag	Char	Expected values: "Y" or "N" "Y" if the subject has a history of gallstones at baseline. Else, "N".
PCOSFL	Polycystic ovary syndrome Flag	Char	Expected values: "Y" or "N" "Y" if the subject has a history of Polycystic ovary syndrome at baseline. Else, "N".
Baseline Biopsy Characteristics			
FIBSCBL	Baseline Fibrosis Score	Char	MI.MIORRES where MIBLFL = "Y", MITESTCD = "FIBROSIS" and MITSTDTL = "NASH CRN FIBROSIS STAGE"
ISHAKBL	Baseline Modified ISHAK Score	Num	MI.MORRES where MIBLFL = "Y", MITESTCD = "FIBROSIS" and MITSTDTL = "ISHAK FIBROSIS SCORE"
STEOBL	Baseline Steatosis Score	Integer	MI.MIORRES where MIBLFL = "Y", MITESTCD = "NAS" and MITSTDTL = "Steatosis"

Variable Name	Variable Label	Type	Comments
HBALLBL	Baseline Hep. Ballooning Score	Integer	MI.MIORRES where MIBLFL = "Y", MITESTCD = "NAS" and MITSTDTL = "Ballooning"
LOBINBL	Baseline Lobular Inflammation Score	Integer	MI.MIORRES where MIBLFL = "Y", MITESTCD = "NAS" and MITSTDTL = "Lobular Inflammation"
PORTFL	Baseline Portal Inflammation	Text	MI.MIORRES where MIBLFL = "Y", MITESTCD = "INFLAM" and MITSTDTL = "Portal Inflammation"
NASBL	Baseline NAS	Integer	Sum of ADSL.STEOBL, ADSL.HBALLBL, ADSL.LOBINFL
NASCAT	Baseline NAS Category	Text	Set to "NAS <6" if ADSL.NASBL<6; Set to "NAS >=6" if ADSL.NASBL>=6
NASCATN	Baseline NAS Category (N)	Integer	Numeric representation of NASCAT. "1" = "NAS <6", "2" = "NAS >=6"
NASFIBFL	Overall Histological Diagnosis of NASH with Fibrosis Flag	Char	Expected Values: "Y" or "N" If MI.MIORRES = "Yes" where MI.MITESTCD = "NASHIND", then "Y". Else, "N"
Non-Invasive Baseline Characteristics			
MELDBL	Baseline MELD Score	Num	RS.RSSTRESN when RS.RSBLFL = "Y" and RSTEST = "MELD01-Score"
FIB4BL	Baseline FIB4	Float	Calculated using lab baseline values and age from Demographics as: Age (years) x AST (U/L)/[Platelet Count (x10^9/L) x ALT^(1/2) (U/L)]
ELFBL	Baseline ELF	Float	MI.MIORRES where MIBLFL = "Y", MITESTCD = "Fibrosis" and MITSTDTL = "Enhanced Liver Fibrosis Score"
APRIBL	Baseline APRI	Float	LB.LBSTRESN where LB.LBBLFL = "Y" and LBTESTCD = "APRI"
Concomitant Medications Characteristics			
LIPCAT	Lipid-Lowering Agents Category	Char	Expected values: "No Concomitant Use", "Prior and Concomitant Use", "New Concomitant Use" Any lipid-lowering agents, including statins
STATCAT	Statins Category	Char	Expected values: "No Concomitant Use", "Prior and Concomitant Use", "New Concomitant Use" Statins only
ANHYPCAT	Antihypertensive Category	Char	Expected values: "No Concomitant Use", "Prior and Concomitant Use", "New Concomitant Use" Antihypertensive medications
ANDIACAT	Antidiabetic Medications Category	Char	Expected values: "No Concomitant Use", "Prior and Concomitant Use", "New Concomitant Use" Any antidiabetic medications, including Thiazolidinediones
TZDCAT	Thiazolidinediones Category	Char	Expected values: "No Concomitant Use", "Prior and Concomitant Use", "New Concomitant Use" Thiazolidinediones only
VITECAT	Vitamin E Category	Char	Expected values: "No Concomitant Use", "Prior and Concomitant Use", "New Concomitant Use" Vitamin E
ANCPCAT	Anticoagulants and Antiplatelets Category	Char	Expected values: "No Concomitant Use", "Prior and Concomitant Use", "New Concomitant Use" Anticoagulants and Antiplatelets

5.2.2 Occurrence Data Structure (OCCDS) Data Sets

Occurrence Data Structure (OCCDS) Data Sets are used for the counting of subjects with a given record or term, and often includes a coding dictionary (e.g., MedDRA for adverse events, WHODrug for concomitant medications)). In creating ADaM OCCDS data sets, sponsors should follow the guidance specified by the ADaM Structure for Occurrence Data,[26] including sections on dictionary coding and categorization variables, timing variables, and flag and indicator variables.

5.2.2.1 Adverse Event Analysis Data Set (ADAE)

Sponsors should include all records from SDTM.AE. If a sponsor uses the approach of recording multiple records in AE each time the event changes in severity, relationship, etc. then this should be noted in the metadata. Also note that the specification includes a flag variable that indicates which record had the worst severity grade for a given adverse event (MedDRA preferred term) when there are multiple occurrences (records) of the same adverse event for the same subject. Sponsors may select a grading scale of their choice, which should be pre-specified in the study protocol. In addition, sponsors should consult the FDA Data Standards Catalog for guidance on the appropriate MedDRA version to use.

To aid evaluation of potential DILI, this specification also includes a Hepatic Injury Flag(s) to flag AEs occurring within defined grouped queries (e.g., Custom MedDRA Queries) and accompanying flags to identify the earliest record within each hepatic injury flag. Sponsors should discuss the exact derivations of the hepatic injury flags with the FDA. Any deviations from the specifications below should be clearly communicated to the review division.

Table 11. ADAE Variables

Variable Name	Variable Label	Type	Comments
TRTEMFL	Treatment-Emergent Analysis Flag	Char	Expected Values: "Y" or null A value of "Y" on a record should indicate a new or worsening AE after the first dose of investigational product. Metadata should be clear on the reference dates that are used to define the period during which an adverse event is considered treatment emergent.
AOCCPIFL	1st Max Sev./Int. Occur Within PT Flag	Char	Expected Values: "Y" or null Character indicator for the first occurrence of the maximum severity/intensity within the subject and preferred term.
HPxxFL	Hepatic Injury xx Flag	Char	Expected values: "Y" or null Sponsors should create Hepatic Injury Flag(s) to capture specific preferred terms within the MedDRA hierarchy. Sponsors should consult FDA regarding how many flags are required and how exactly to derive each flag.
HPFxxFL	First Hepatic Injury xx Flag	Char	Expected values: "Y" or null

[26] Available at https://www.cdisc.org/standards/foundational/adam/adamig-v1-1-release-package.

Variable Name	Variable Label	Type	Comments
			Create one additional flag for each HPxxFL flag created and flag the earliest (min ASTDY) on treatment (ASTDY >= 1) for each subject and record that fits the criteria. Otherwise, null
DILIFL	Potential DILI Event Flag	Char	Expected values: "Y" or null Flag the following Adverse Events as "Y": Fatigue, Nausea, Vomiting, Abdominal pain or tenderness, Fever, Rash, Pruritus, Jaundice/icterus, Altered mental status
DILIPFL	Potential DILI Event Flag (30-days prior)	Char	Expected values: "Y", "N" or null Null for records where DILIFL is null. For records with DILIFL = "Y": if the event occurs in the 30 days before a lab-identified DILI threshold met in the ADDILI data set, then "Y". Else, "N"
DILIAFL	Potential DILI Event Flag (30-days after)	Char	Expected values: "Y","N" or null Null for records where DILIFL is null. For records identified with DILIFL = "Y": if the event occurs in the 30 days after a lab-identified DILI threshold met in the ADDILI data set, then "Y". Else, "N"

5.2.3 Basic Data Structure (BDS) Data Sets

The following guidance should be used to create data sets that fall within the BDS structure (e.g., ADLB to display laboratory data). Specific guidelines are included for several BDS data sets. All BDS data sets should use the guidelines provided below, which have been written in accordance with the ADaM Implementation Guide.

All BDS Data Sets should contain the identifier variables, record-level treatment and dose variables, and timing variables as specified in the ADaM Implementation Guide specifically the section as it relates to the ADaM Basic Data Structure (in ADaMIG v1.1, Section 3.3).

5.2.3.1 Laboratory Analysis Data Set (ADLB)

The following issues are considerations for the creation and content of the laboratory analysis data set. Sponsors should follow the ADaM Basic Data Structure (BDS) model when creating this data set. Visit windowing and/or inclusion of unscheduled visits should be included in this analysis data set (liver-related lab results should be included for all scheduled and unscheduled visits). When records are imputed or derived in any manner, the standard ADaM variable, DTYPE should be used. All tests and records included in the SDTM.LB domain should be carried into the ADLB data set, and sponsors should also include a derived parameter for the calculated R value. Sponsors should provide a clear derivation method for their calculation of the R value.

It is acceptable for a sponsor's ADLB data set to contain additional parameters beyond those noted above. Similarly, variables in addition to those described below may be included.

CDER strongly encourages sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units

might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. If conversion of units is performed, the sponsor should clearly indicate the units that the data was originally collected in. For more information on CDER/CBER current thinking on conventional units, please see the FDA *Study Data Technical Conformance Guide* available on the FDA Study Data Standards Resources webpage. FDA requests laboratory test results be presented in both SI units and US conventional units.

The ADLB specifications listed below include four important variables for the analysis of drug-induced liver injury: DILIBLFL, PEAKFL, REDUCEFL, and ONSETFL. These flags look for DILI records at their baseline, peak (maximum post-baseline), washout (50% reduction after reaching maximum post-baseline), and onset (first sign of potential DILI). There are many different ways to define the onset of liver injury; Sponsors should refer to the existing guidance for industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (July 2009) and seek agreement with the FDA review division on how to specify the onset of DILI injury for their study.

Table 12. ADLB Variables

Variable Name	Variable Label	Type	Comments
DILIFL	Drug-Induced Liver Injury Flag	Char	Expected Value: "Y" or null This flag should have "Y" for the following records: • ALT, AST, ALP, GGT, Total Bilirubin, Direct Bilirubin, INR records AND • The evaluable record for each test at each visit. If more than one record is collected at each visit, a derived record should be created with DTYPE = "AVERAGE". The average record should be flagged, and the individual records used to create the average record should not be flagged. Unscheduled visits may also be flagged as "Y". Else, null
ABLFL	Analysis Baseline Flag	Char	Expected Value: "Y" or null Character indicator to identify the baseline record for each subject and parameter. Sponsors should confirm with the FDA review division on an appropriate definition for baseline. Examples may include flagging the last record prior to treatment or deriving a new baseline record as the average of all pre-treatment records for a given subject and parameter.
DILIBLFL	DILI Baseline Flag	Char	Expected Value: "Y" or null For each subject and liver biochemistry parameter, flag the baseline record used for DILI analysis as "Y". This flag is similar to ABLFL, however, in subjects with elevated transaminase levels at enrollment who show improvements in their transaminase levels and in essence, establish a new lower baseline during the trial, sponsors should use the new lower transaminase values in subsequent assessment for potential DILI (and subsequently using this flag to identify the record used in

Variable Name	Variable Label	Type	Comments
			baseline calculations for DILI analyses). Sponsors should seek review division agreement and provide clear guidance in their ADRG or define.xml file on derivations for alternate baseline calculations and provide a flag in the ADSL to indicate if any subjects have discrepancies between ABLFL and DILIBLFL for any liver biochemistry parameter.
DTYPE	Derivation Type	Char	For the case where there are multiple observations and an average or a geometric mean will be used for the observation for the visit window in the analysis instead of a single selected real observation. If this is the case, a new record should be created, and the records identified by having some values for these records in DTYPE variable. The possible value could be "AVERAGE", or "GEOMETRIC", or other meaningful values. This should be explained in the define file or SAP.
R2ANRHI	Ratio to Analysis Range Upper Limit	Num	Ratio to the upper limit of the analysis range. Equal to AVAL / ANRHI.
R2BASE	Ratio to Baseline Value	Num	Ratio to the baseline value. Equal to AVAL / BASE. If used for a given PARAM, should be populated for all post-baseline records of that PARAM regardless of whether that record is used for analysis.
ANL01FL	Analysis Record Flag 01	Char	Expected Values: "Y" or null Flag the records to be used in analysis. If multiple records are recorded for a parameter at the same visit, use this flag to indicate which record should be used. Derived records (if it was appropriate to take an average of two records) may be flagged as "Y". Sponsors should provide a clear derivation for how they choose to derive this flag.
ANL02FL	Analysis Record Flag 02	Char	Expected Values: "Y" or null Flag the maximum post-baseline record for each subject and parameter as "Y"
ANL03FL	Analysis Record Flag 03	Char	Expected Values: "Y" or null Flag the minimum post-baseline record for each subject and parameter as "Y"
PEAKFL	DILI Peak Flag	Char	Expected Values: "Y", "N" or null Null for all pre-treatment records and records where DILIFL = "N". If ANL02FL = "Y" and DILIFL = "Y", then "Y". Otherwise, "N"
REDUCEFL	DILI Reduction Flag	Char	Expected Values: "Y", "N" or null Null for all pre-treatment records and records where DILIFL = "N". Flag the first record after PEAKFL for each subject and parameter in which AVAL is equal to or less than 50% of the value of AVAL where PEAKFL = "Y"
ONSETFL	DILI Lab Onset Flag	Char	Expected Values: "Y" or null Sponsors should discuss an appropriate definition of DILI onset with DHN. The agreed upon definition should be pre-specified in the study protocol. Based on the agreed upon definition, flag all DILI records as "Y" at a given visit when the onset trigger has been met. *For example, if ONSET is determined as the first time a subject's ALT or AST value reaches >= 3x ULN with concurrent TB >= 2x ULN within 30 days of the ALT or AST elevation, when a subject does reach that threshold, all DILI records (ALT, AST, ALP, TB, DB, GGT) from that visit should be flagged as "Y".*
LASTFL	Last Record Per Parameter Flag	Char	Expected Values: "Y" or null Flag the last record (max ADY) for each subject and parameter. NOTE: this is not limited to last on-treatment record; this may include follow-up records.

5.2.3.2 Drug Induced Liver Injury Analysis Data Set (ADDILI)

This custom data set will be used to analyze subjects for potential DILI. Sponsors should seek agreement with the FDA review division on the appropriate parameters to use for DILI assessments. This data set contains variables that seek a maximum value within "xx" days. Sponsors should discuss with the FDA the appropriate time window (e.g., 30 days) to use.

For any subject meeting the sponsor-established criteria for potential DILI, two additional parameters should be created – one to provide the outcome and another to provide the action taken as a result of potential DILI.

Sponsors may include additional parameters as they see fit and should consult with FDA if the review division requires other parameters specific for the review. Additionally, this data set includes a set of flag variables that identifies any procedure(s) and/or workups performed to evaluate a subject for potential DILI. These flag variables may be derived from the SDTM.PR (Procedures), SDTM.LB, or SDTM.MB domains (or other domains as determined by the sponsor).

The ADDILI data set should include the basic demographic information, treatment variables, start and end date variables, and baseline lab characteristics variables from the ADSL data set.

Table 13. ADDILI Variables

Variable Name	Variable Label	Type	Comments
PARAM	Parameter	Char	Expected values: "Potential DILI" and "Outcome of Potential DILI", "Action Taken from Potential DILI"
PARAMCD	Parameter Code	Char	• For PARAM = Potential DILI: "DILI" • For PARAM = Outcome of Potential DILI – Outcome: "OUTDILI" • For PARAM = Action Taken from Potential DILI= "ACNDILI"
AVAL	Analysis Value	Num	Expected Values: 1 or 0 *Note: The criteria below are example criteria for evaluation of DILI. Sponsors may consult the FDA for appropriate criteria for their study.* Example 1: PARAMCD = "DILI": • If ALTULNMX >= 3 and TBALTMX >= 2 and ALPALTMX < 2, then 1 OR • If ASTULNMX >= 3 and TBASTMX >= 2 and ALPASTMX < 2, then 1 • Else 0 Example 2: PARAMCD = "DILI": • If ALPULNMX >= 2 and TBALPMX >= 2, then 1

Variable Name	Variable Label	Type	Comments
			• Else 0
AVALC	Analysis Value (C)	Char	If AVAL = 1, then "Y"; if AVAL = 0, then "N" For PARAMCD = "OUTDILI" • Expected values: "FATAL", "NOT RECOVERED/NOT RESOLVED". "RECOVERED/RESOLVED", "RECOVERED/RESOLVED WITH SEQUELAE", "RECOVERING/RESOLVING", "UNKNOWN" For PARAMCD = "ACNDILI": • Expected values: "DOSE INCREASED", "DOSE NOT CHANGED", "DOSE RATE REDUCED", "DOSE REDUCED", "DRUG INTERRUPTED", "DRUG WITHDRAWN", "NOT APPLICABLE", "UNKNOWN"
ALTULNMX	Post-Baseline Maximum Ratio ALT/ULN	Num	For each subject, ADLB.R2ANRHI where ADLB.PEAKFL = "Y" and ADLB.PARAMCD = "ALT"
ALTBLMX	Post-Baseline Maximum Ratio ALT/BL	Num	For each subject, ADLB.AVAL where ADLB.PEAKFL = "Y" and ADLB.PARAMCD = "ALT" / ADLB.AVAL where ADLB.DILIBL = "Y" and ADLB.PARAMCD = "ALT"
ASTULNMX	Post-Baseline Maximum Ratio AST/ULN	Num	For each subject, ADLB.R2ANRHI where ADLB.PEAKFL = "Y" and ADLB.PARAMCD = "AST"
ASTBLMX	Post-Baseline Maximum Ratio AST/BL	Num	For each subject, ADLB.AVAL where ADLB.PEAKFL = "Y" and ADLB.PARAMCD = "AST" / ADLB.AVAL where ADLB.DILIBL = "Y" and ADLB.PARAMCD = "AST"
ALPULNMX	Post-Baseline Maximum Ratio ALP/ULN	Num	For each subject, ADLB.R2ANRHI where ADLB.PEAKFL = "Y" and ADLB.PARAMCD = "ALP"
ALPBLMX	Post-Baseline Maximum Ratio ALP/BL	Num	For each subject, ADLB.AVAL where ADLB.PEAKFL = "Y" and ADLB.PARAMCD = "ALP" / ADLB.AVAL where ADLB.DILIBL = "Y" and ADLB.PARAMCD = "ALP"
TBALTMX	Post-Baseline Maximum Ratio TB/ULN following ALTULNMX	Num	For each subject, max value of ADLB.R2ANRHI where ADLB.PARAMCD = "TB" within **xx** days after post-baseline maximum ALT value.
TBASTMX	Post-Baseline Maximum Ratio TB/ULN following ASTULNMX	Num	For each subject, max value of ADLB.R2ANRHI where ADLB.PARAMCD = "TB" within **xx** days after post-baseline maximum AST value.
TBALPMX	Post-Baseline Maximum Ratio TB/ULN following ALPULNMX	Num	For each subject, max value of ADLB.R2ANRHI where ADLB.PARAMCD = "TB" within **xx** days after post-baseline maximum ALP value.
ALPALTMX	Max ALP/ULN Ratio after Max ALT/ULN Ratio	Num	For each subject, max value of ADLB.R2ANRHI where ADLB.PARAMCD = "ALP" within **xx** days after post-baseline maximum ALT value.
ALPASTMX	Max ALP/ULN Ratio after Max AST/ULN Ratio	Num	For each subject, max value of ADLB.R2ANRHI where ADLB.PARAMCD = "ALP" within **xx** days after post-baseline maximum AST value.
RVAL	R Value	Num	ADLB.AVAL where ADLB.PARAMCD = "R"
DILI Workup Flags			
ALCHFL	Alcohol Assessment Flag	Char	Expected Values: "Y", "N", or null If Alcohol information was collected and reported in the SDTM.SU domain as a result of potential DILI injury, then "Y". If alcohol information was not collected as a result of potential DILI injury, then "N". If unknown, null
HEPFL	Hepatitis Serology Flag	Char	Expected Values: "Y", "N", or null

Variable Name	Variable Label	Type	Comments
			If Hepatitis Serology information was collected and reported in the SDTM.MB domain as a result of potential DILI injury, then "Y". If Hepatitis Serology information was not collected as a result of potential DILI injury, then "N". If unknown, null
AUTOIFL	Auto-Immune Serology Flag	Char	Expected Values: "Y", "N", or null If Auto-Immune Serology information was collected and reported in the SDTM.LB domain as a result of potential DILI injury, then "Y". If Auto-Immune Serology was not performed as a result of potential DILI injury, then "N". If unknown, null
ULTRAFL	Ultrasound Flag	Char	Expected Values: "Y", "N", or null If an ultrasound was performed and reported in the SDTM.PR as a result of potential DILI injury, then "Y". If an ultrasound was not performed as a result of potential DILI injury, then "N". If unknown, null
CTFL	CT Scan Flag	Char	Expected Values: "Y", "N", or null If a CT scan was performed and reported in the SDTM.PR as a result of potential DILI injury, then "Y". If a CT scan was not performed as a result of potential DILI injury, then "N". If unknown, null
MRIFL	MRI Flag	Char	Expected Values: "Y", "N", or null If an MRI was performed and reported in the SDTM.PR as a result of potential DILI injury, then "Y". If an MRI was not performed as a result of potential DILI injury, then "N". If unknown, null
BIOPFL	Biopsy Flag	Char	Expected Values: "Y", "N", or null If a biopsy was conducted and reported in the SDTM.PR as a result of potential DILI injury, then "Y". If a biopsy was not performed as a result of potential DILI injury, then "N". If unknown, null
ERCPFL	ERCP Flag	Char	Expected Values: "Y", "N", or null If an ERCP was performed and reported in the SDTM.PR as a result of potential DILI injury, then "Y". If an ERCP was not performed as a result of potential DILI injury, then "N". If unknown, null
MRCPFL	MRCP Flag	Char	Expected Values: "Y", "N", or null If a MRCP was performed and reported in the SDTM.PR as a result of potential DILI injury, then "Y". If a MRCP was not performed as a result of potential DILI injury, then "N". If unknown, null
LVTRNSFL	Liver Transplant Flag	Char	Expected Values: "Y", "N", or null If a liver transplant was performed and reported in the SDTM.PR as a result of potential DILI injury, then "Y". If a liver transplant was not performed as a result of potential DILI injury, then "N". If unknown, null
OTHPRFL	Other Procedure Flag	Char	Expected Values: "Y", "N", or null If another procedure was performed as the result of potential DILI injury, then "Y". If no other procedure was performed as the result of potential DILI injury, then "N". If unknown, null

5.2.3.3 Microscopic Findings Analysis Data Set (ADMI)

The Microscopic Findings Analysis Data Set contains histological data used to support accepted efficacy determination in noncirrhotic NASH development programs. AVALC is the primary variable used to support the analysis. This data set should be derived primarily from the Microscopic Findings (SDTM.MI) data set and should contain additional parameters discussed with the FDA during the pre-NDA process to assess all histological endpoints. This data set follows the ADaM BDS.

The ADMI data set should include the basic demographic information, treatment variables, start and end date variables, and baseline biopsy characteristics variables from the ADSL data set.

Table 14. ADMI Variables

Variable Name	Variable Label	Type	Comments
Biopsy Parameter Information			
PARAM	Parameter	Text	The ADMI data set should contain all records from the SDTM.MI domain. In addition, the sponsor should create records with parameters to evaluate the histological endpoints, with results captured in the appropriate AVAL/AVALC variable. An example parameter may be: "Improvement of Fibrosis Stage with No Worsening of NASH". In this case, sponsors should consider the results from the Fibrosis Stage and NASH score between the baseline and end of treatment biopsies.
PARAMCD	Parameter Code	Text	Short Code for PARAM. Sponsors may choose an appropriate parameter code for the derived parameters that evaluate the histological endpoints.
MITSTDTL	Microscopic Examination Detail	Text	MI.MITSTDTL
PARCAT1	Parameter Category 1	Text	MI.MICAT for records coming from MI data set. For derived parameters evaluating histological endpoints, create an appropriate category (i.e., "Primary histological endpoint", "Secondary efficacy endpoint", etc.)
Analysis Information			
AVAL	Analysis Value	Num	Transferred from either MI.MISTRESN or MI.MIORRES
AVALC	Analysis Value I	Text	Transferred from MI.MISTRESC for character tests (i.e. Definite NASH)
AVALCAT1	Analysis Category 1	Text	It may be appropriate to categorize results of certain tests. For example, the sponsor may decide it is important to separate Lobular Inflammation results of 0 and 1 from results greater than one. In that case, for records with PARAM = Lobular Inflammation, AVALCAT would take values of either "Lobular Inflammation score 0 to 1" or "Lobular Inflammation greater than 1". Additional variables may be created (AVALCAT2, AVALCAT3, etc.) as necessary.

Variable Name	Variable Label	Type	Comments
Criteria Evaluation			
CRIT1	Analysis Criterion 1	Text	NOTE: This is an example of a criteria that may be used for analysis. Specific criterion to include in this data set should be discussed with the FDA, as this may change on a study-by-study basis. Should more than one criterion be required, used CRIT2/CRIT2FL, CRIT3/CRIT3FL, etc. *Where PARAMCD is "HCYTBALL", "LOBINF", "MODISHAK", "NASHCRN", "NASHHBLN", "NLOBI", "SAFACT", "STEATOS" indicates criteria of interest as "Improvement of histological feature by at least 1 point/stage"*
CRIT1FL	Criterion 1 Evaluation Result Flag	Text	Set to "Y" if CRIT1 satisfied; else set to "N"
Other Flags			
ABLFL	Analysis Baseline Flag	Text	Set to "Y" for last non-missing record for each value of PARAMCD prior to TRTSDT
ANL01FL	Analysis Record Flag 01	Text	Set to "Y" for the baseline record and the records closest to the target day within the visit target interval as defined by the study metadata.

5.2.3.4 Non-Invasive Serum Biomarkers of Liver Fibrosis and NASH Analysis Data Set (ADRS)

The Non-Invasive Serum Biomarkers of Liver Fibrosis and NASH Analysis Data Set contains information to support additional secondary efficacy endpoints based on non-invasive serum biomarkers of liver fibrosis and NASH (e.g., MELD, FIB-4, ELF, APRI). The MELD score should be provided for noncirrhotic NASH trials. Sponsors should consult with the FDA regarding additional tests that may be required for submission.

AVAL is the primary variable used to support the analysis. This data set should be derived primarily from the Clinical Classifications and Disease Response (SDTM.RS) data set, though many of the tests are calculations based on measurements collected in the Laboratory (SDTM.LB) domain. This data set also contains flags based on the results of derived parameters in the ADMI data set. This data set follows the ADaM Basic Data Structure (BDS).

The ADRS data set should include the basic demographic information, treatment variables, start and end date variables, baseline biopsy characteristics, and non-invasive baseline characteristics variables from the ADSL data set.

Table 15. ADRS Variables

Variable Name	Variable Label	Type	Comments
Parameter Information			
PARAM	Parameter	Text	The ADRS data set should contain all records from the SDTM.RS and SDTM.LB domains for the following example tests: • MELD Score • FIB-4 Score • ELF Score • APRI Score In addition, the sponsor should create records with parameters to evaluate the study's endpoints, with results captured in the appropriate AVAL/AVALC variable. An example parameter may be: "MELD Score from Baseline =<12 to >15". In this case, sponsors should consider a subjects' baseline MELD score and their maximum post-baseline record. If their baseline record was less than 12 and their maximum post-baseline record was greater than or equal to 15, AVALC would return a value of "Y" for this parameter. This is purely an example parameter – sponsors should create their own parameters in consultation with the FDA review division and the endpoints of their study.
PARAMCD	Parameter Code	Text	Short Code for PARAM
Analysis Information			
AVAL	Analysis Value	Num	Transferred from either LB.LBSTRESN or RS.RSSTRESN. For derived parameters that evaluate a specific endpoint, "1" if the endpoint criteria are met or "0" if the endpoint criteria are not met.
AVALC	Analysis Value (C)	Text	Character value of AVAL. For derived parameters that evaluate a specific endpoint, AVALC is "Y" if the endpoint criteria are met. Otherwise, null.
Biopsy Responder Flag(s)			
RESP01FL	First Primary Endpoint Responder Flag	Text	This flag is derived from the ADMI data set. For each derived parameter in ADMI, create one flag (starting with RESP01FL, and then RESP02FL, RESP03FL, etc.) that take values of "Y" or "N" based on whether the subject meets the criteria of the derived parameter. For example, if a parameter in ADMI is "Improvement of Fibrosis Stage with No Worsening of NASH" and the subject met that criteria in ADMI (AVALC = "Y"), then set RESP01FL = Y. The specific parameter being evaluated should be listed in the comments for each parameter in define.xml.

Variable Name	Variable Label	Type	Comments
Other Flags			
DTYPE	Derivation Type	Text	If multiple readings are taken at a given visit, create a new record if appropriate that takes the average measurements of the other records for that parameter at that visit. DTYPE in this case would take a value of "AVERAGE".
ABLFL	Analysis Baseline Flag	Text	Set to "Y" for last non-missing record for each value of PARAMCD prior to TRTSDT
ANL01FL	Analysis Record Flag 01	Text	Flag records used for analysis. Note: This may differ from study-to-study, but one example definition may be: "Flag baseline record and post-baseline records closest to the target day within the visit target interval listed in the study metadata."
Criteria Evaluation			
CRIT1	Analysis Criterion 1	Text	Use this flag to support any derived parameters for this data set. For the example parameter listed under PARAM, the corresponding CRIT1 may take a value of "MELD < 12" where PARAM = "MELD01-Score"
CRIT1FL	Criterion 1 Evaluation Result Flag	Text	Set to "Y" if CRIT1 satisfied; else set to "N"
CRIT2	Analysis Criterion 2	Text	Use this flag to support any derived parameters for this data set. For the example parameter listed under PARAM, the corresponding CRIT1 may take a value of "MELD > 15" where PARAM = "MELD01-Score"
CRIT2FL	Criterion 2 Evaluation Result Flag	Text	Set to "Y" if CRIT1 satisfied; else set to "N"

5.2.4 Time-to-Event Analysis Data Set

The Time to Event Analysis Data Set contains all records needed to support time-to-event analysis for noncirrhotic NASH endpoints and DILI. AVAL is the primary variable used to support the analysis. Sponsors should follow the ADaM Basic Data Structure for Time-to-Event Analyses[27] when creating this data set. The description of the analysis parameter (PARAM) contains the unit of measurement where results are captured in AVAL.

The time-to-event data set should include records for all subjects, including subjects who did not experience an event defined by PARAM. For a subject who did not experience a specific type of event, the subject's time to event is considered 'right-censored', where the value of AVAL represents the length of time between the starting point and the end of the observation period (e.g., the duration of the study for that subject). The numeric Censor (CNSR) variable is used to distinguish whether a subject experienced an event between the defined starting point and the end of the observation period.

When supporting analyses as listed in the examples below, ADTTE may be sourced from ADAE, ADMI, ADDILI and ADSL (or elsewhere). Sponsors should consult FDA to determine

[27] https://www.cdisc.org/standards/foundational/adam/adamig-v1-1-release-package.

the appropriate parameters and their corresponding derivations to be collected and submitted in this data set.

Sponsors should provide clear explanations in the ADaM define.xml for how AVAL is derived for each parameter. In some cases, such as Time to Death, it may look at ASTDY for one record. For other parameters where multiple records should be evaluated to determine if the subject has met the endpoint, the derivation for AVAL may be more complicated. For example, a Time to Peak Lab Washout for DILI parameter needs to consider both when the subject's labs "peak" as well as when those peaks reach a "washout" state–in this case, sponsors could use values of ADY when ADLB.PEAKFL and ADLB.REDUCEFL = 'Y' to calculate AVAL in ADTTE.

Examples of applicable analyses to support safety and efficacy analyses may include:

Table 16. Example Time to Event Parameters

PARAMCD	**PARAM**[28, 29]	**AVAL**
HPCIRRH	Time to Histological Progression to Cirrhosis (days)	*Propose derivations for each parameter*
HEPDCE	Time to Hepatic Decompensation Event (days)	
ASCREQTR	Time to Ascites requiring treatment (days)	
HEPENC	Time to Hepatic Encephalopathy at least West Haven grade 2 or above requiring hospitalization (days)	
VARHEM	Time to Variceal hemorrhage requiring hospitalization (days)	
OTHCDE	Time to Other Clinical Decompensation Event (e.g., Spontaneous Bacterial Peritonitis) (days)	
LVRTRNS	Time to Liver Transplant (days)	
DEATH	Time to Death (days)	
ONSETDIL	Time to Onset Potential DILI Injury (days)	
WASHOUT	Time to Peak Lab Washout for DILI (days)	

[28] Per the ADaM Basic Data Structure for Time-to-Event Analyses, PARAM in the ADTTE may be longer than 40 characters (maximum 200). See https://www.cdisc.org/standards/foundational/adam/adam-basic-data-structure-bds-time-event-tte-analyses-v1-0.

[29] The examples listed below are measured in days. Sponsors should use their judgement in determining the appropriate unit of measurement.

APPENDIX

Example ADLB and ADDILI Data Sets

Consider the sample Laboratory Analysis Data Set (ADLB) and Drug-Induced Liver Injury Analysis Data Set (ADDILI) tables below for Subject ABC-123. This example only shows one subject's alanine aminotransferase (ALT) values; however, for the purposes of this example, assume the subject's aspartate aminotransferase (AST) and/or total bilirubin (TB) values indicate the subject is a potential drug-induced liver injury (DILI) candidate as identified by pre-established criteria between the sponsor and the U.S. Food and Drug Administration (FDA) (example criteria noted in the ADDILI section of this document). As a reminder, these criteria are sample criteria. Sponsors should consult with FDA to establish appropriate criteria to evaluate DILI. Below is a list of other considerations for this sample data set:

- In this example, the subject has two pre-baseline lab readings. These lab reading are averaged to create a new baseline record for each parameter.

- Onset DILI (ONSETFL = "Y") is defined in this example as the first visit in which a subjects' ALT > 3x ULN. This happens on Study Day 14 (assume ANRHI = 55.0). Sponsors may use their own definition for Onset DILI after consultation with the FDA review division.

- Reduced Flag (REDUCEFL = "Y") may only occur after a subject has reached their peak (PEAKFL = "Y") for a given subject and parameter.

- The example ADDILI data set only contains the variables pertinent to ALT; sponsors should follow the guidance provided in the ADDILI section of this document for the full list of variables to be provided.

- For the example ADDILI data set, ALTULNMX is calculated as the maximum post-baseline ALT value divided by the upper limit of normal (197.0 / 55.0 = 3.58). ALTBLMX is calculated as the maximum post-baseline ALT value divided by the DILI baseline value (197.0 / 52.5 = 3.75).

Table A. Subset of Sample ADLB

PARAMCD	AVAL	BASE	ADY	ABLFL	ANL02FL	ANL03FL	PEAKFL	REDUCEFL	ONSETFL	LASTFL
ALT	51.0		-8							
ALT	54.0		1							
ALT	52.5			Y						
ALT	95.0	52.5	7				N	N		
ALT	197.0	52.5	14		Y		Y	N	Y	
ALT	191.0	52.5	21				N	N		
ALT	92.0	52.5	28				N	Y		
ALT	73.0	52.5	35			Y	N	N		Y

Table B. Subset of Sample ADDILI

PARAM	AVALC	ALTULNMX	ALTBLMX
Potential DILI	Y	3.58	3.75
Outcome of Potential DILI	RECOVERED/RESOLVED	3.58	3.75
Action Taken from Potential DILI	DOSE REDUCED	3.58	3.75

Example MI and SUPPMI Domains

Consider the sample Microscopic Findings (MI) and Supplemental Microscopic Findings (SUPPMI) domains below for Subject ABC-123. This subject has two biopsies, one at baseline and one at end of treatment, each with two Pathologists reviewing. Any disagreement between the histopathological assessment between the Pathologists results in an adjudication committee making a final determination (as shown with Microscopic Findings Test (MITEST) = ‘FIBROSIS’ during the first biopsy). The data set should also include standard

variables such as STUDYID, DOMAIN, MIDTC, and MIDY as noted in the SDTM Implementation Guide.[1] The sample below only contains a few measurements; sponsors should refer to the MI section of this document for the complete list of recommended and permissible parameters to be collected from the biopsy.

This example domain uses MIREFID as the identifier for the slide being analyzed, but sponsors should use identifier variables available from the SDTMIG to label biopsies and slides cut from the biopsy. The linkage between the identifier variables should be made clear in the define.xml and/or Study Data Reviewers Guide (SDRG) files. Linkages between individual biopsies and/or slides and other domains such as Biospecimen Findings (BS) or Biospecimen Events (BE) should be connected via a RELREC domain.

The SUPPMI domain shows the adequacy of the slides. The slide evaluated during the baseline biopsy was deemed adequate, and the end of treatment biopsy was deemed not adequate due to both a blurred image and cracked slide. As such, the MIACPTFL variable is null for the end of treatment biopsy as these records were not accepted for the analysis due to the inadequate slide.

Table C. Subset of Sample MI Domain

MIREFID	MITEST	MITSTDTL	MIORRES	MIACPTFL	MIEVAL	MIEVALID	VISIT
SPEC001	NAFLD Activity Score	TOTAL SCORE	5		PATHOLOGIST	PATHOLOGIST 1	BASELINE
SPEC001	Fibrosis	NASH CRN FIBROSIS STAGE	Moderate zone 3		PATHOLOGIST	PATHOLOGIST 1	BASELINE
SPEC001	NAFLD Activity Score	TOTAL SCORE	5		PATHOLOGIST	PATHOLOGIST 2	BASELINE
SPEC001	Fibrosis	NASH CRN FIBROSIS STAGE	Mild zone 3		PATHOLOGIST	PATHOLOGIST 2	BASELINE
SPEC001	NAFLD Activity Score	TOTAL SCORE	5	Y	ADJUDICATION COMMITTEE	ADJUDICATOR	BASELINE
SPEC001	Fibrosis	NASH CRN FIBROSIS STAGE	Moderate zone 3	Y	ADJUDICATION COMMITTEE	ADJUDICATOR	BASELINE
SPEC002	NAFLD Activity Score	TOTAL SCORE	5		PATHOLOGIST	PATHOLOGIST 1	END OF TREATMENT

[1] Available at https://www.cdisc.org/standards/foundational/sdtmig/sdtmig-v3-3.

MIREFID	MITEST	MITSTDTL	MIORRES	MIACPTFL	MIEVAL	MIEVALID	VISIT
SPEC002	Fibrosis	NASH CRN FIBROSIS STAGE	Mild zone 3		PATHOLOGIST	PATHOLOGIST 1	END OF TREATMENT
SPEC002	NAFLD Activity Score	TOTAL SCORE	5		PATHOLOGIST	PATHOLOGIST 2	END OF TREATMENT
SPEC002	Fibrosis	NASH CRN FIBROSIS STAGE	Mild zone 3		PATHOLOGIST	PATHOLOGIST 2	END OF TREATMENT

Table D. Subset of Sample SUPPMI Domain

IDVAR	IDVARVAL	QLABEL	QVAL
MIREFID	SPEC001	Overall Image Quality	Adequate
MIREFID	SPEC002	Overall Image Quality	Not Adequate
MIREFID	SPEC002	Image Condition	MULTIPLE
MIREFID	SPEC002	Image Condition 1	CRACKED SLIDE
MIREFID	SPEC002	Image Condition 2	BLURRY IMAGE