

Designing an ADaM Dataset for Streamlined Drug-Induced Liver Injury Screening Analyses

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ABSTRACT

The FDA's release of the Standard Safety Tables and Figures - Integrated Guideline (ST&F) in August 2022 introduced default screening analyses for Drug-Induced Liver Injury (DILI). These analyses include the hepatocellular DILI screening plot, the cholestatic DILI screening plot, and a comparison of patients with maximal treatment-emergent liver test abnormalities. Implementing these analyses consistently across studies requires an analysis-ready, standards-based data structure.

This paper presents a fit-for-purpose, CDISC-compliant Analysis Data Model (ADaM) Basic Data Structure (BDS)-based dataset design for DILI screening analyses within the FDA ST&F workflow, with an emphasis on programming efficiency, analytical flexibility, and traceability. The proposed ADDILI structure is designed to support the FDA ST&F DILI screening analyses while simplifying derivations and downstream table and figure programming.

Concrete data examples illustrate how the proposed structure simplifies the derivation of required endpoints and graphics, reduces repetitive programming, and enhances traceability. Adoption of this ADaM design will promote consistency, interoperability, and regulatory readiness in DILI screening and reporting across studies.

INTRODUCTION

Drug-Induced Liver Injury (DILI) represents one of the most significant safety concerns in drug development. Based on the 2009 FDA Guidance for Industry "Drug-Induced Liver Injury: Premarketing Clinical Evaluation", Hy's Law cases are characterized by three key components: (1) evidence that the drug causes hepatocellular injury, generally shown by a higher incidence of aminotransferase (AT) elevations above 3x the upper limit of normal (ULN) compared to control; (2) cases among trial subjects showing AT elevation often far greater than 3x ULN combined with elevation of serum total bilirubin (TB) to >2x ULN without significant elevation of alkaline phosphatase (ALP); and (3) no other reason to explain the combination of increased AT and TB, such as viral hepatitis or other hepatotoxic drugs.

The FDA has released several guidelines related to DILI screening and reporting, including: (1) Standard Safety Tables and Figures (ST&F) Integrated Guide (2022 and 2025); and (2) Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Nonalcoholic Steatohepatitis (NASH), 2021. These guidelines introduce new methods that enhance the screening of potential DILI signals, including potential Hy's Law cases, cholestasis, and Temple's Corollary.

To support robust and consistent DILI signal detection and regulatory compliance within the FDA ST&F workflow, an analysis-ready ADaM dataset can help simplify and standardize the generation of DILI tables and figures. This paper describes a fit-for-purpose, BDS-based ADaM dataset (ADDILI), designed specifically for the FDA ST&F DILI screening workflow. ADDILI extends conventional ADaM laboratory dataset structures by organizing cross-parameter liver safety logic such as peak value selection, time-window based relationships among liver tests, multi-parameter DILI criteria, and source-record traceability into a single analysis-ready dataset. This dedicated structure is needed because FDA ST&F DILI analyses depend not only on individual laboratory results, but also on the timing and combined interpretation of AT, TB, and ALP results. ADDILI enables consistent, efficient, and traceable generation of FDA standard safety tables and figures for DILI analyses.

FDA ST&F LIVER INJURY SCREENING ANALYSES

The liver injury screening analyses defined in the FDA ST&F Integrated Guide are part of the **Laboratory Analyses** within the **Core Safety Tables and Figures**. This core section comprises standard, routine safety analyses that are expected to support safety evaluation and should be generated for the ST&F package.

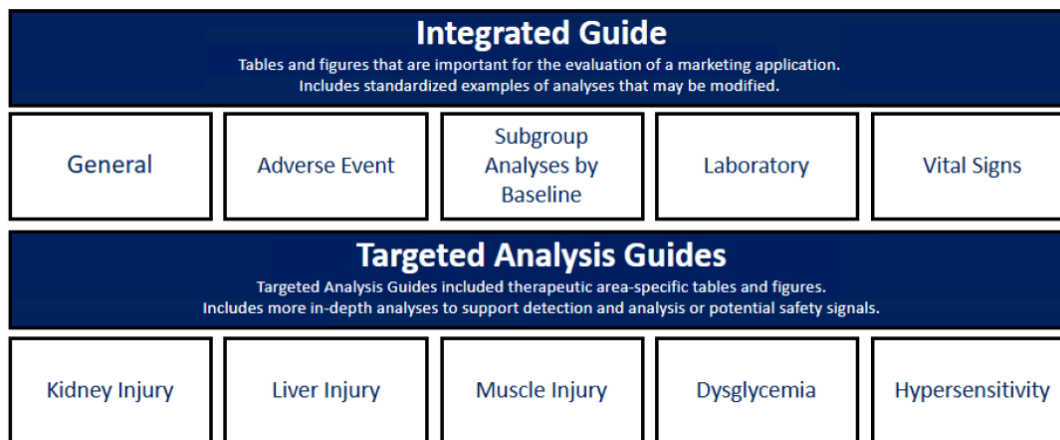


Figure 1: Standard Safety Tables and Figures Organization

The liver injury screening analyses include four analyses:

- **Missing and Existing Data Analysis (plot)**
- **Hepatocellular DILI Screening Plot**
- **Cholestatic DILI Screening Plot**
- **Comparison of Subjects with Maximal Treatment-Emergent Liver Test Abnormalities (table)**

Since the missing data analysis is not confined to liver injury and is also applicable to other lab tests and vital signs, the ADDILI dataset does not cover that analysis. The remaining three analyses are described below.

HEPATOCELLULAR DILI SCREENING PLOTS

The primary purpose of the hepatocellular DILI screening plot is to identify subjects with potential hepatocellular DILI that has led to sufficient liver damage (approaching 50% of the total liver volume) to result in decreased bilirubin excretion and cause jaundice. Such hepatocellular jaundice due to DILI is considered a "Hy's Law" case, which can carry a 10% to 50% mortality from acute liver failure. Hy's Law cases may only constitute a small fraction of all subjects with hepatocellular DILI, so the size of the study population needs to be sufficiently large to detect these cases. The presence of even one or two such cases may be sufficient to jeopardize drug approval or raise concerns for postmarketing safety.

In the default plot, each subject is plotted based on their maximum post-baseline total bilirubin (TB, y-axis) and transaminase (ALT or AST, whichever is higher, x-axis). Each value is expressed as multiples of ULN. Dashed lines represent TB and transaminase cutoffs of 2x ULN and 3x ULN (default), respectively, based on Hy's Law criteria.

For purposes of this plot, potential Hy's Law cases are defined as *any post-baseline TB elevation to $\geq 2x$ ULN occurring on or within 30 days after a post-baseline ALT or AST elevation to $\geq 3x$ ULN, with concurrent ALP $< 2x$ ULN*. These patients are identified in the graph with a red circle. Patients may appear in the right upper quadrant based on maximum post-baseline TB and AST or ALT but should not be identified as a potential Hy's Law case (not circled) if the elevations did not occur within the prespecified time frame (i.e., within 30 days) and/or the concurrent ALP level was $\geq 2x$ ULN.

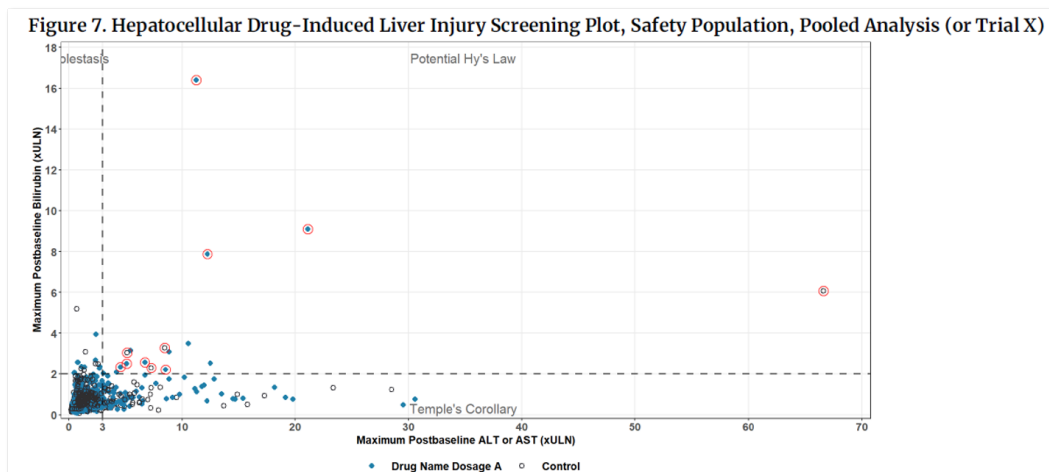


Figure 2: Hepatocellular DILI Screening Plot (FDA ST&F Integrated Guide, 2025)

CHOLESTATIC DILI SCREENING PLOT

While ALP elevations can be attributed to other sources (e.g., bone), significant ALP elevation in the setting of hepatic dysfunction (e.g., jaundice) may suggest cholestatic DILI. The cholestatic screening plot is analogous to the hepatocellular screening plot and is intended to quickly identify cases of possible serious cholestatic DILI.

Maximum post-baseline TB is plotted against maximum post-baseline ALP rather than ALT or AST. The quadrants are similarly defined by TB >2x ULN, but the ALP cutoff is >2x ULN as the default. Red circled cases in the right upper quadrant indicate subjects who had their maximum bilirubin within 30 days (default) of ALP becoming >2x ULN. Cases in the right upper quadrant are not considered Hy's Law cases, nor are cases in the right lower quadrant considered Temple's Corollary cases. These labels do not apply to the cholestatic plot.

Nevertheless, the combination of ALP >2x ULN and jaundice is concerning for cholestatic injury deserving exploration. Similar to the hepatocellular screening plot, the cholestatic screening plot provides a visual assessment of imbalances between arms and numbers of cases by quadrants.

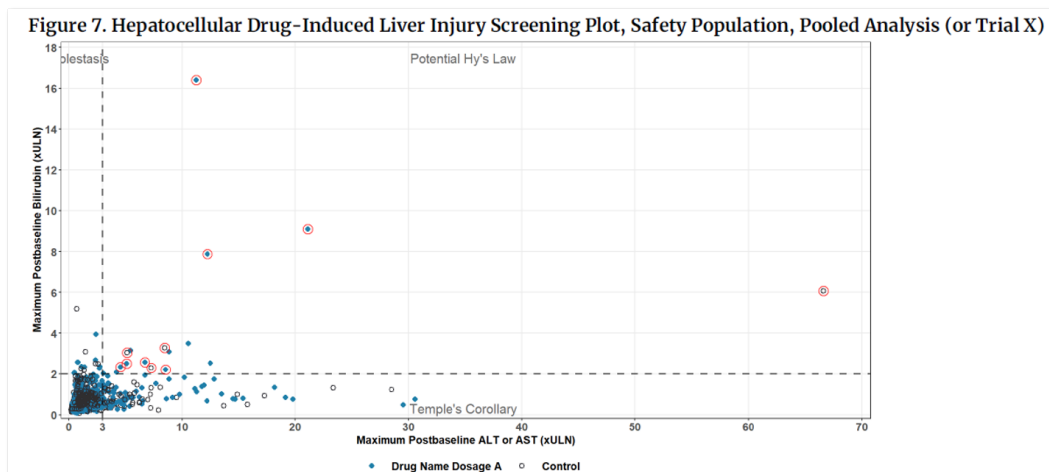


Figure 3: Cholestatic DILI Screening Plot (FDA ST&F Integrated Guide, 2025)

COMPARISON OF SUBJECTS WITH MAXIMAL TREATMENT-EMERGENT LIVER TEST ABNORMALITIES

Table 21 (Subjects in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot) and Table 22 (Subjects in Quadrants of Interest for Potential Cholestatic DILI Screening Plot) in the FDA ST&F Integrated Guide (2025) are intended to demonstrate potential imbalances in the subjects found in each quadrant of concern between trial arms using maximum treatment-emergent liver test abnormalities. These tables help differentiate potential hepatocellular and cholestatic DILI cases between trial arm groups. Each row in these tables corresponds to a quadrant in the hepatocellular or cholestatic plots.

Quadrant	Drug Name Dosage A N=XXX n/Ns (%)	Control N=XXX n/Ns (%)
Potential Hy's Law (right upper quadrant)	X/Y (Z)	X/Y (Z)
Cholestasis (left upper quadrant)	X/Y (Z)	X/Y (Z)
Temple's corollary (right lower quadrant)	X/Y (Z)	X/Y (Z)
Total	X/Y (Z)	X/Y (Z)

Figure 4: Subjects in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot (FDA ST&F Integrated Guide, 2025)

Quadrant	Drug Name Dosage A N=XXX n/Ns (%)	Control N=XXX n/Ns (%)
BILI $\geq 2x$ ULN and ALP $\geq 2x$ ULN (right upper quadrant)	X/Y (Z)	X/Y (Z)
BILI $\geq 2x$ ULN and ALP $< 2x$ ULN (left upper quadrant)	X/Y (Z)	X/Y (Z)
BILI $< 2x$ ULN and ALP $\geq 2x$ ULN (right lower quadrant)	X/Y (Z)	X/Y (Z)
Total	X/Y (Z)	X/Y (Z)

Figure 5: Subjects in Quadrants of Interest for Potential Cholestatic DILI Screening Plot (FDA ST&F Integrated Guide, 2025)

ADDILI DATA STRUCTURE

The proposed ADDILI dataset follows the standard ADaM Basic Data Structure (BDS). It contains both source parameters carried over from SDTM liver injury-related lab tests (**ALT**, **AST**, **BILI**, **ALP**) and derived parameters (**ATBILALP**, **ALPBIL**, **ATBILMAX**, **APBILMAX**) specifically designed for the DILI screening analyses.

Table 1: ADDILI Parameters Overview summarizes the parameters in the ADDILI dataset, their origin, and their purpose in the DILI screening analyses.

PARAMCD	PARAM	Origin	Purpose
ALT	Alanine Aminotransferase	SDTM	Derive ATBILALP; plot individual points in Hepatocellular plot
AST	Aspartate Aminotransferase	SDTM	
BILI	Bilirubin	SDTM	Derive ATBILALP and ALPBIL; plot individual points in both Hepatocellular and Cholestatic plots
ALP	Alkaline Phosphatase	SDTM	Derive ALPBIL; plot individual points in Cholestatic plot
ATBILALP	Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase	Derived	Draw red circles in Hepatocellular plot
ALPBIL	Alkaline Phosphatase and Bilirubin	Derived	Draw red circles in Cholestatic plot
ATBILMAX	AST or ALT and BILI Maximum Postbaseline	Derived	Count subjects by quadrants in Hepatocellular table
APBILMAX	ALP and BILI Maximum Postbaseline	Derived	Count subjects by quadrants in Cholestatic table

Table 1: ADDILI Parameters Overview

Table 2 ADDILI Variables Overview provides the key variables included in the proposed ADDILI structure and summarizes their labels, types, and derivation rules.

Variable	Label	Type	Derivation
USUBJID	Unique Subject Identifier	Char	ADSL.USUBJID
ADT	Analysis Date	Integer	Date part of LB.LBDTC in SAS numeric format. Missing for derived parameters.
PARAMCD	Parameter Code	Char	Refer to Table 1: ADDILI Parameters Overview
PARAM	Parameter	Char	Refer to Table 1: ADDILI Parameters Overview
PARCAT1	Parameter Category 1	Char	Set to "ALT or AST" for PARAMCD in ("ALT", "AST"); otherwise, set to the same value of PARAMCD.
AVAL	Analysis Value	Integer	ALT, AST, BILI, ALP: LB.LBSTRESN ATBILMAX: map per row order in Figure 4: Subjects in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot (FDA ST&F Integrated Guide, 2025) APBILMAX: map per row order in Figure 5: Subjects in Quadrants of Interest for Potential Cholestatic DILI Screening Plot (FDA ST&F Integrated Guide, 2025)
AVALC	Analysis Value (C)	Char	ATBILALP, ALPBIL: combines the R2ANRHI (ratio) values from each source parameter ATBILMAX, APBILMAX: map per row labels in hepatocellular and cholestatic tables
ABLFL	Baseline Record Flag	Char	Set to "Y" for the last non-missing record on or prior to first does date for each subject and parameter. Set to missing for derived parameters.
DILIBLFL	DILI Baseline Flag	Char	Derived for each subject and parameter: 1) If there exists a record with ANL03FL = 'Y', then DILIBLFL is set to 'Y' on that record. 2) If no such record is found, DILIBLFL is set to 'Y' on the record where ABLFL = 'Y'. Set to missing for derived parameters.
R2ANRHI	Ratio to Normal Range Upper Limit	Float	If ANRHI is not missing and not equal to 0, then R2ANRHI = AVAL / ANRHI. Set to missing for derived parameters.
PEAKFL	Peak Flag	Char	Derive within each subject and each PARCAT1. Set to "Y" for the records with the highest non-missing post-baseline R2ANRHI. Set to missing for derived parameters.
ANL01FL	Analysis Flag 01	Char	ALT, AST, BILI, ALP: retrieve records where PEAKFL = "Y", if multiple records are selected, set ANL01FL to "Y" for the earliest record. ATBILALP, ALPBIL: Set to "Y" for the records where CRIT1FL = "Y"; if there are multiple records, select the first one for each subject.

Variable	Label	Type	Derivation
ANL02FL	Analysis Flag 02 (Baseline Abnormal)	Char	Select the record where ABLFL = 'Y', if AVAL > ANRHI, then ANL02FL = 'Y' for this record. Set to missing for derived parameters.
ANL03FL	Analysis Flag 02 (Improve from Baseline)	Char	For each subject and parameter: 1) Find the record where ABLFL = 'Y' and ANL02FL = 'Y'. 2) For subjects identified in step (1), find the immediate post-baseline lab record. If this record satisfies $ANRLO \leq AVAL \leq ANRHI$, then set ANL03FL to 'Y' for this record. 3) If no new lower baseline is found, ANL03FL will be missing. Set to missing for derived parameters.
CRIT1	Analysis Criterion 1	Char	• ALT, AST: set to '$\geq 3 \times \text{ULN}$'. • BILI, ALP: set to '$\geq 2 \times \text{ULN}$'. • ATBILALP: set to '$AT \geq 3 \times \text{ULN}$ and $BILI \geq 2 \times \text{ULN}$ and $ALP < 2 \times \text{ULN}$'. • ALPBIL: set to '$ALP \geq 2 \times \text{ULN}$ and $BILI \geq 2 \times \text{ULN}$'.
CRIT1FL	Criterion 1 Evaluation Result Flag	Char	Set to 'Y' if the R2ANRHI for each parameter on the same record satisfies the criteria; otherwise, if at least one parameter value is not missing, set to 'N'.
ASPID	Analysis Identifier	Char	ASPID is created by concatenating PARAMN and sequence number for each record by dash ('-'). Set to missing for derived parameters.
ARELID	Analysis Relationship Identifier	Char	ARELID is created by concatenating the ASPID of the contributing parameters separated by comma (",").

Table 2 ADDILI Variables Overview

VARIABLE DERIVATIONS FOR SOURCE PARAMETERS (ALT, AST, BILI AND ALP)

To identify the records used for generating figures and tables and to support the derivation of derived parameters, a series of variables are created in the ADDILI dataset (e.g., analysis flags) including the definition of the important concept of new DILI baseline.

New DILI Baseline Definition

The FDA ST&F Integrated Guide states: "In patients with elevated baseline transaminase values, who show improvements in their transaminase levels and in essence, establish a new lower baseline during the trial, consider using the new lower transaminase values in subsequent assessment for potential DILI." The FDA NASH technical specification further elaborates that sponsors should flag the baseline record used for DILI analysis and provide clear guidance on derivations for alternate baseline calculations.

To accommodate the possible re-baseline scenarios for certain lab tests (e.g., ALT, AST), the following variables are introduced to identify those subjects:

- **ANL02FL** (Analysis Flag 02 - Baseline Abnormal): Select the baseline record. If $AVAL > ANRHI$ at baseline, then ANL02FL = 'Y' for this record.
- **ANL03FL** (Analysis Flag 03 - Improve from Baseline): For each subject and parameter, derived using the following steps: (1) Find the last record on or prior to first treatment where ANL02FL = 'Y'; (2) For subjects identified in step 1, find the immediate next lab record after initial treatment. If this record has AVAL returning to normal ($ANRLO \leq AVAL \leq ANRHI$), set ANL03FL to 'Y' for this record; (3) Otherwise, ANL03FL will be missing for this parameter.
- **DILIBLFL** (DILI Baseline Flag): Derived for each subject and parameter. If there exists a record with ANL03FL = 'Y', then DILIBLFL is set to 'Y' on that record. Otherwise, DILIBLFL is set to 'Y' on the

record where ABLFL = 'Y' (traditional baseline).

- DILIBASE** and **R2DLBASE**: Baseline value and ratio to baseline for post-baseline records based on the new definition of DILI baseline (DILIBLFL). In subjects with abnormal baseline test results, the Integrated Guide mentions that a separate DILI screening plot using the ratio to baseline (R2DLBASE) values on the X and Y-axis can be generated.

Using the DILI baseline identified by DILIBLFL, post-baseline records are selected relative to this updated baseline rather than the traditional baseline. This approach combines both cases: subjects without normalizing after treatment and subjects who normalized after treatment.

Figure 6 presents the derivation flow for the DILI baseline flag (DILIBLFL), which identifies the baseline record to be used for DILI-specific analyses. The flowchart illustrates how the traditional baseline (ABLFL) is retained when appropriate, and how a new DILI baseline is assigned when an abnormal baseline value is followed by an immediate post-treatment value returning to the normal range.

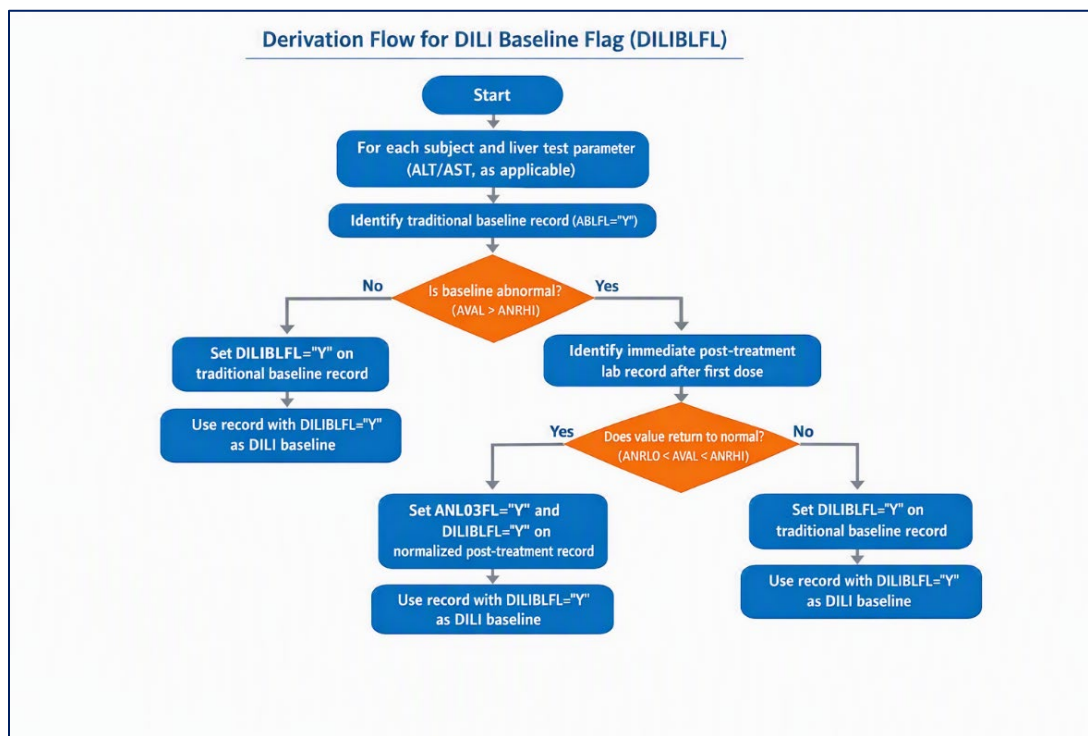


Figure 6 Derivation Flow for DILI Baseline Flag (DILIBLFL)

Figure 7: Comparison of Traditional Baseline (ABLFL) vs. DILI Baseline (DILIBLFL) illustrates the comparison between the traditional baseline (ABLFL) and the new DILI baseline (DILIBLFL) for the re-baseline scenario. The example shows that when an abnormal baseline normalizes immediately after treatment, the normalized post-treatment record becomes the DILI baseline for subsequent DILI-specific analyses.

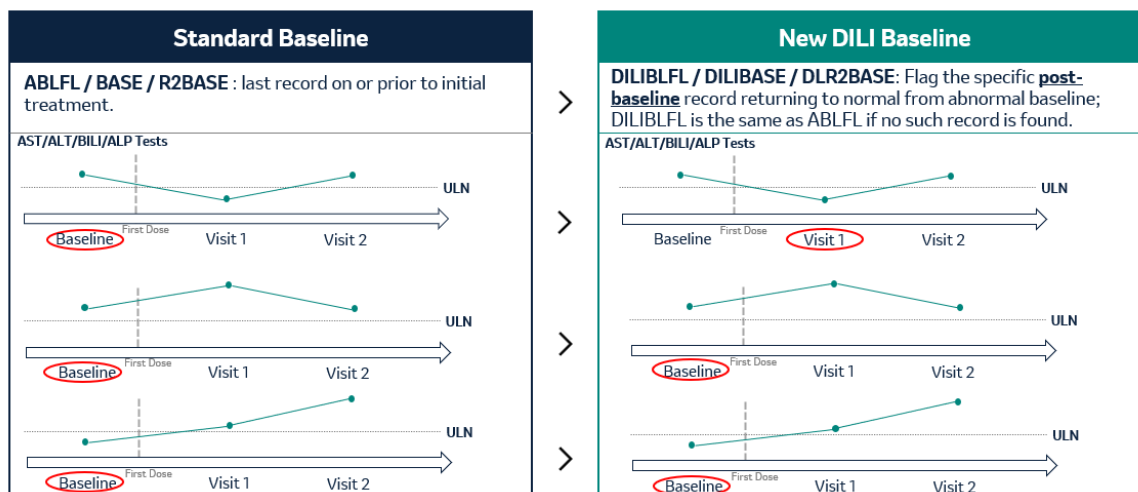


Figure 7: Comparison of Traditional Baseline (ABLFL) vs. DILI Baseline (DILIBLFL)

Maximum Post-Baseline Selection

The individual dots on the hepatocellular and cholestatic figures represent the maximum post-baseline record for those relevant lab tests. Two new flags (**PEAKFL**, **ANL01FL**) are created to help identify those records.

- **PARCAT1**: For the hepatocellular plot, the X-axis represents the maximum post-baseline ALT or AST, so a new variable PARCAT1 is created to group ALT and AST together (valued as 'ALT or AST') for identifying peak records. For other tests, PARCAT1 equals PARAMCD.
- **PEAKFL**: After grouping, the maximum post-baseline ratio of test results (AVAL) to upper limit of normal (ANRHI) is selected per subject, per PARCAT1. This flag may select multiple records if the maximum post-baseline R2ANRHI value is the same across records.
- **ANL01FL** (Analysis Flag 01): To pick one unique record for analysis, ANL01FL is created to pick one per subject per PARCAT1. The individual dots in the plot are selected using this analysis flag.

Criterion Setting

Corresponding to the reference lines (3x ULN for ALT or AST, 2x ULN for BILI and ALP), the criterion variables (**CRIT1**, **CRIT1FL**) are created. As per ADaM-IG, criterion variables can vary across parameters within a dataset, so CRIT1 is valued differently for each parameter. CRIT1FL denotes whether **R2ANRHI** (=AVAL / ANRHI) is above the relevant threshold for each parameter.

PARAMCD	CRIT1	CRIT1FL
ALT	>=3 x ULN	"Y" if R2ANRHI >= 3; "N" if R2ANRHI < 3
AST	>=3 x ULN	"Y" if R2ANRHI >= 3; "N" if R2ANRHI < 3
BILI	>=2 x ULN	"Y" if R2ANRHI >= 2; "N" if R2ANRHI < 2
ALP	>=2 x ULN	"Y" if R2ANRHI >= 2; "N" if R2ANRHI < 2

Table 3: Criterion Variable Definitions by Parameter

Traceability Construction

Traceability is one of ADaM's fundamental principles when deriving new parameters. Before creating the derived parameters, a new traceability variable for ALT, AST, BILI, and ALP called **ASPID** is created, which will be used to create another traceability variable called **ARELID** for those derived parameters.

ASPID is created by first sorting the lab records by USUBJID, PARAMCD, and ADT, then assigning a sequence number starting from 1 per subject, per parameter. ASPID is created by concatenating PARAMN and the sequence number with a dash ('-'). For example, if PARAMN for ALT is 1, the first ALT record for a subject would have ASPID = '1-1'.

Summary of Source Parameter Derivations

With the new baseline, maximum post-baseline flag, criterion variables, and traceability variables derived, the individual dots on the figures can be easily selected for each subject. The traceability linkage has also been built for use in derived parameters.

Table 4: Data Example for Source Parameters provides a data example illustrating how these variables work together for one subject across all four source parameters.

USUBJID	PARAMCD	PARCAT1	ADT	ABLFL	DILIBLFL	R2ANRHI	PEAKFL	ANL01FL	ANL02FL	ANL03FL	CRIT1	CRIT1FL	ASPID
ABC-001	ALT	ALT or AST	2024-04-02	Y		2.6			Y		>=3 x ULN	N	1-1
ABC-001	ALT	ALT or AST	2024-04-20		Y	0.9				Y	>=3 x ULN	N	1-2
ABC-001	ALT	ALT or AST	2024-05-05			4.1	Y	Y			>=3 x ULN	Y	1-3
ABC-001	AST	ALT or AST	2024-04-02	Y	Y	0.5					>=3 x ULN	N	2-1
ABC-001	AST	ALT or AST	2024-04-20			3.9					>=3 x ULN	Y	2-2
ABC-001	AST	ALT or AST	2024-05-05			4.1	Y				>=3 x ULN	Y	2-3
ABC-001	BILI	BILI	2024-04-02	Y	Y	1.4			Y		>=2 x ULN	N	3-1
ABC-001	BILI	BILI	2024-04-20			1.8					>=2 x ULN	N	3-2
ABC-001	BILI	BILI	2024-05-05			2.3	Y	Y			>=2 x ULN	Y	3-3
ABC-001	ALP	ALP	2024-04-02	Y	Y	1.7			Y		>=2 x ULN	N	4-1
ABC-001	ALP	ALP	2024-04-20			2.2	Y	Y			>=2 x ULN	Y	4-2
ABC-001	ALP	ALP	2024-05-05			1.5					>=2 x ULN	N	4-3

Table 4: Data Example for Source Parameters

Key observations from this data example:

- **Baseline definitions:** For ALT, the subject is abnormal at baseline (ANL02FL = 'Y'). At the immediate post-baseline visit, the subject returned to normal, so ANL03FL is set to 'Y' reflecting improvement. Thus ABLFL and DILIBLFL differ for ALT. For AST, BILI, and ALP, no re-baseline scenario applies.
- **Maximum post-baseline selections:** ALT and AST are grouped under the same PARCAT1 ('ALT or AST'). The maximum post-baseline R2ANRHI = 4.1 appears on multiple records. ANL01FL = 'Y' is set on the earliest record to identify one unique record for plotting.
- **Criterion flags:** CRIT1FL is set to 'Y' when R2ANRHI exceeds the parameter-specific cutoff, and 'N' when below.
- **Traceability:** ASPID is built combining PARAMN and sequence number for later use in derived parameter linkage.

DERIVED PARAMETERS FOR ANALYSES (ATBILALP, ALPBIL, ATBILMAX, APBILMAX)

There are two sets of derived parameters (four total): one set (ATBILALP, ATBILMAX) for the hepatocellular analyses and another set (ALPBIL, APBILMAX) for the cholestatic analyses. The general approach is similar between the two sets, so we focus on explaining the hepatocellular parameters in detail.

Derived Parameter	Source Parameters
ATBILALP	ALT, AST, BILI, ALP
ALPBIL	ALP, BILI
ATBILMAX	ALT, AST, BILI
APBILMAX	ALP, BILI

Table 5: Derived Parameters and Their Source Components

Parameter for Potential Hy's Law Cases (Red Circle)

The derived parameter **ATBILALP** identifies cases of potential Hy's Law and is used to generate the red circles in the plot's upper right quadrant. As per the FDA ST&F Integrated Guide, the potential Hy's Law logic is defined as: *any post-baseline TB elevation to $\geq 2x$ ULN occurring on or within 30 days after a post-baseline ALT or AST elevation to $\geq 3x$ ULN, with concurrent ALP $< 2x$ ULN*. Since this logic involves three existing parameters, as per ADaM-IG principles, a function of more than one parameter should be added as a new parameter.

The derivation selects any post-baseline ALT or AST records, joins them with BILI records within 30 days, and also joins them with ALP records within 30 days after ALT or AST. This results in multiple joined records per subject. Due to the multiple-record nature of this parameter, a new traceability variable **ARELID** is created by concatenating the **ASPID** values of the source parameters (ALT/AST, BILI, and ALP) separated by commas. This variable functions similarly to --SEQ variables used in ADaM datasets and can trace back to the exact lab test records that form this derived parameter.

Since the joined records only consider time window restrictions (BILI and ALP within 30 days after ALT/AST), we need to determine if the lab test values meet the threshold cutoff for potential Hy's Law cases. The criterion variables are used as follows: **CRIT1** = 'AT $\geq 3 \times$ ULN and BILI $\geq 2 \times$ ULN and ALP $< 2 \times$ ULN', and **CRIT1FL** = 'Y' when all conditions are met. If multiple records per subject satisfy the criteria, ANL01FL is set to "Y" on one selected record per subject for red circle generation.

Note: This parameter identifies subjects for which the dot on the plot is to be circled. The maximum values plotted for a subject may not be the values that resulted in the classification of the subject as a potential Hy's Law case (red circle).

Parameter for Maximal Abnormality Table

The comparison table shows frequency counts of subjects found in each quadrant of concern between trial arms using maximum post-baseline values, selected by **ANL01FL** for lab tests (ALT, AST, and BILI).

To support efficient table generation, the derived parameter ATBILMAX is structured as one record per subject. The logic selects the maximum post-baseline values for ALT or AST and for BILI using **ANL01FL**, then merges them to form the final record. The **AVALC** value is derived based on the **CRIT1FL** values for ALT/AST and BILI, mapping to the appropriate quadrant as shown in **Table 6: AVALC/AVAL Mapping for Parameter ATBILMAX**.

CRIT1FL (ALT or AST)	CRIT1FL (BILI)	AVALC	AVAL
Y	Y	Potential Hy's Law (right upper)	1
N	Y	Cholestasis (left upper)	2
Y	N	Temple's Corollary (right lower)	3
N	N	Normal (left lower)	4

Table 6: AVALC/AVAL Mapping for Parameter ATBILMAX

Summary of Derived Parameters

The derived parameters greatly streamline generation of the hepatocellular and cholestatic plots and tables by representing potential Hy's Law cases as clear parameters and providing readily usable parameters for table generation. Clear linkage to original lab tests is also built through the novel traceability variable **ARELID**.

Table 7: Data Example for Derived Parameters provides a data example for the derived parameters ATBILALP and ATBILMAX, showing how the source parameter records combine to form these new parameters.

USUBJID	PARAMCD	AVALC	AVAL	ANL01FL	CRIT1	CRIT1FL	ARELID
ABC-001	ATBILALP	ALTRATIO=0.9, BILIRATIO=1.8, ALPRATIO=2.2			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	1-2, 3-2, 4-2
ABC-001	ATBILALP	ALTRATIO=0.9, BILIRATIO=1.8, ALPRATIO=1.5			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	1-2, 3-2, 4-3
ABC-001	ATBILALP	ALTRATIO=0.9, BILIRATIO=2.3, ALPRATIO=2.2			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	1-2, 3-3, 4-2
ABC-001	ATBILALP	ALTRATIO=0.9, BILIRATIO=2.3, ALPRATIO=1.5			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	1-2, 3-3, 4-3
ABC-001	ATBILALP	ALTRATIO=4.1, BILIRATIO=1.8, ALPRATIO=2.2			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	1-3, 3-2, 4-2
ABC-001	ATBILALP	ALTRATIO=4.1, BILIRATIO=1.8, ALPRATIO=1.5			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	1-3, 3-2, 4-3
ABC-001	ATBILALP	ALTRATIO=4.1, BILIRATIO=2.3, ALPRATIO=2.2			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	1-3, 3-3, 4-2
ABC-001	ATBILALP	ALTRATIO=4.1, BILIRATIO=2.3, ALPRATIO=1.5		Y	AT >=3xULN and BILI >=2xULN and ALP <2xULN	Y	1-3, 3-3, 4-3
ABC-001	ATBILALP	ALTRATIO=3.9, BILIRATIO=1.8, ALPRATIO=2.2			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	2-2, 3-2, 4-2
ABC-001	ATBILALP	ALTRATIO=3.9, BILIRATIO=1.8, ALPRATIO=1.5			AT >=3xULN and BILI >=2xULN and ALP <2xULN	Y	2-2, 3-2, 4-3
ABC-001	ATBILALP	ALTRATIO=3.9, BILIRATIO=2.3, ALPRATIO=2.2			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	2-2, 3-3, 4-2
ABC-001	ATBILALP	ALTRATIO=3.9, BILIRATIO=2.3, ALPRATIO=1.5			AT >=3xULN and BILI >=2xULN and ALP <2xULN	Y	2-2, 3-3, 4-3

USUBJID	PARAMCD	AVALC	AVAL	ANL01FL	CRIT1	CRIT1FL	ARELID
ABC-001	ATBILALP	ALTRATIO=4.1, BILIRATIO=1.8, ALPRATIO=2.2			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	2-3, 3-2, 4-2
ABC-001	ATBILALP	ALTRATIO=4.1, BILIRATIO=1.8, ALPRATIO=1.5			AT >=3xULN and BILI >=2xULN and ALP <2xULN	Y	2-3, 3-2, 4-3
ABC-001	ATBILALP	ALTRATIO=4.1, BILIRATIO=2.3, ALPRATIO=2.2			AT >=3xULN and BILI >=2xULN and ALP <2xULN	N	2-3, 3-3, 4-2
ABC-001	ATBILALP	ALTRATIO=4.1, BILIRATIO=2.3, ALPRATIO=1.5			AT >=3xULN and BILI >=2xULN and ALP <2xULN	Y	2-3, 3-3, 4-3
ABC-001	ATBILMAX	Potential Hy's Law (right upper)	1				1-3, 3-3

Table 7: Data Example for Derived Parameters

Key observations from this data example:

- Parameter **ATBILALP**:
 - Any post-baseline records for ALT, AST, BILI and ALP are joined as long as the time window is satisfied (BILI and ALP within 30 days after ALT/AST). 4 ALT/AST records join with 2 BILI records and 2 ALP records, resulting in 16 ATBILALP records.
 - The criterion variable (CRIT1) involves criteria from three sources: ALT/AST, BILI, and ALP. CRIT1FL = 'Y' when all conditions are satisfied simultaneously.
 - To streamline the selection of one unique record for drawing the red circle, ANL01FL = 'Y' is set on one record that satisfies the criteria (earliest from source parameters).
 - AVALC combines the R2ANRHI (ratio) values from each source parameter to aid data review.
 - The traceability variable ARELID combines the ASPID values from source parameters, making it easy to link back to the original records used in the derivation.
- Parameter **ATBILMAX**: The maximum post-baseline records for ALT or AST (ASPID = '1-3') and BILI (ASPID = '3-3') are selected using ANL01FL. Based on their R2ANRHI values, AVALC and AVAL are mapped per Table 7.

CUSTOMIZATIONS

Beyond the default FDA ST&F DILI screening analyses, the FDA ST&F Integrated Guide describes additional customization options based on study-specific needs, including optional liver biochemistry analyses. The proposed ADDILI structure provides a core framework that can be extended for these analyses by reusing existing variables, adding analysis-specific flags, and deriving additional criterion variables as needed. Two examples are described below.

MULTIPLES OF BASELINE ANALYSES

For studies enrolling subjects with abnormal baseline liver biochemistry values, additional plots may be generated using multiples of baseline rather than multiples of ULN. The ADDILI structure can be adapted for this customization by using **ANL02FL** to identify subjects with elevated baseline AST, ALT, or ALP values and **R2DLBASE** to provide ratio-to-DILI-baseline values for plotting. This approach enables the same analysis-ready framework to accommodate both ULN-based and baseline-based DILI screening displays.

LAST VALUE ON-TREATMENT ANALYSES

The “last value on-treatment” is defined as the final observation for a given laboratory parameter within a pre-specified on-treatment time window. The definition of this time window should consider study-specific factors such as trial design, drug half-life, and the use of concomitant medications. The FDA ST&F Integrated Guide includes the table “*Subjects With Last On-Treatment Chemistry Value $\geq$ Level 2 Criteria by Treatment Arm*” to support this analysis. For liver biochemistry, the Level 2 criteria are predefined thresholds applied to key parameters (e.g., AST, ALT, ALP, and BILI).

For implementation of this analysis, the ADDILI data structure can be extended to include derived criterion variables (e.g., CRIT2, CRIT2FL) to indicate whether Level 2 thresholds are met. In addition, a dedicated analysis flag (e.g., ANL04FL) can be introduced to identify the last on-treatment record based on study-specific definitions. This flag would be set to “Y” for records that simultaneously satisfy the definition of last on-treatment and meet the Level 2 criteria, thereby enabling consistent derivation of the corresponding summary table.

Liver biochemistry
Alkaline phosphatase, high (U/L) >2.0X ULN
Alanine aminotransferase, high (U/L) >5.0X ULN
Aspartate aminotransferase, high (U/L) >5.0X ULN
Total bilirubin, high (mg/dL) >2.0X ULN

Figure 8: Liver Biochemistry Level 2 Criteria Table

CONCLUSION

This paper presents a fit-for-purpose, CDISC-compliant ADaM dataset design (ADDILI) specifically tailored for FDA ST&F DILI screening analyses. The key contributions of this design are:

- **Standardized data structure:** The ADDILI dataset provides a consistent BDS-based framework that is designed for all three FDA ST&F DILI screening analyses (hepatocellular plot, cholestatic plot, and maximal abnormality comparison tables) within a single dataset.
- **Simplified derivations:** The introduction of derived parameters (ATBILALP, ALPBIL, ATBILMAX, APBILMAX) reduces complex multi-parameter logic into readily-usable records that feed directly into figure and table generation with minimal additional programming.
- **Enhanced traceability:** The novel traceability variables (ASPID, ARELID) maintain clear linkage from derived parameters back to their source lab test records, ensuring transparency and auditability.
- **Regulatory readiness:** The design accommodates the FDA's re-baseline concept (DILIBLFL) and aligns with both the FDA ST&F guideline and the NASH technical specification, promoting regulatory compliance.

Adoption of this ADaM design will promote consistency, interoperability, and regulatory readiness in DILI screening and reporting across studies. Future work may extend this approach to additional liver safety endpoints or adapt the structure for disease-specific populations. By converting complex cross-parameter DILI screening logic into standardized, traceable ADaM records, the proposed ADDILI design enables more consistent, efficient, and review-ready implementation of FDA ST&F liver injury analyses.

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