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

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Meet the Speaker

Ben Gao

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Ben Gao, M.Sc., is a statistical programmer with MSD China. He has been working on late phase oncology studies with experiences in analysis reporting and e-submission. He previously worked as data manager and SDTM programmer at PAREXEL, and has work experiences from database design, data cleaning and SDTM implementation. He is interested in adopting CDISC data standards and utilizing new languages (R, Python) to streamline daily work.

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- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author(s) have no real or apparent conflicts of interest to report.*

Agenda

1. Background and Overview
2. FDA ST&F DILI Analyses
3. ADDILI Data Structure

Background and Overview

Drug-Induced Liver Injury (DILI)

- DILI is a term for liver damage that can occur as a side effect of certain medications
- Liver injuries are typically categorized based on the pattern of liver enzyme elevations
- Patterns of injury
  - **Hepatocellular**: characterized by a primary increase in alanine aminotransferase (ALT), an enzyme found mainly in the liver. A hepatocellular injury suggests damage to the liver cells (hepatocytes)
  - **Cholestatic**: characterized by a primary increase in alkaline phosphatase (ALP), an enzyme related to the bile ducts. A cholestatic pattern suggests damage to the bile ducts, which can lead to a backup of bile in the liver
  - **Mixed**: shows increases in both ALT and ALP. It suggests a mixed pattern of damage involving both the liver cells and the bile ducts

FDA ST&F DILI Analyses

- DILI screening Analyses are within Laboratory Analyses of the **Standard Safety Tables and Figures section**

- DILI section is comprised of 4 default screening analyses:
  - **Missing and Existing Data Analysis**
  - **Hepatocellular DILI Screening Plot**
  - **Cholestatic DILI Screening Plot**
  - **Comparison of Patients with Maximal Treatment-Emergent Liver Test Abnormalities**

- Missing and Existing Data Analysis is not covered in this proposed ADDILI since it is not limited to lab (e.g., vital signs) or liver function tests.

FDA ST&F DILI Analyses

Hepatocellular DILI Screening Plots

Purpose:

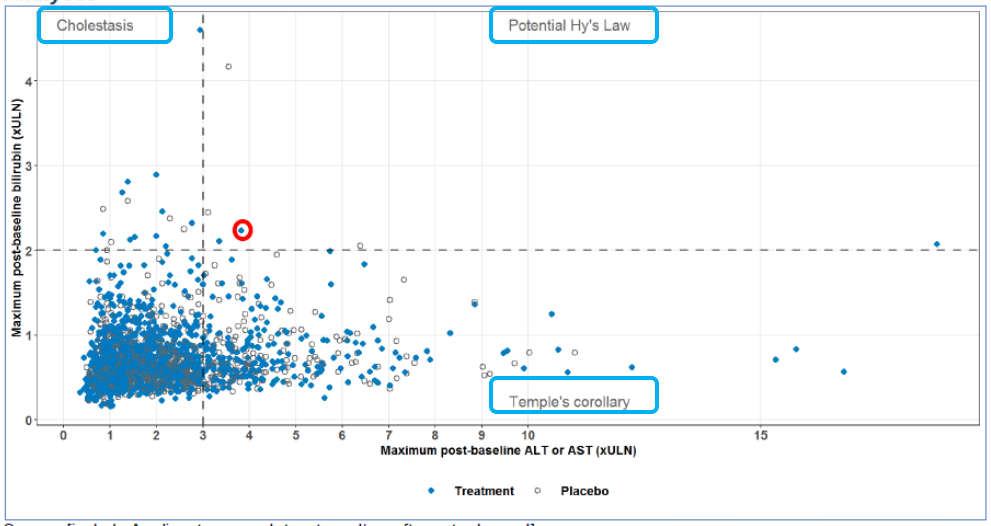
- Quickly identify cases of potential serious hepatocellular DILI that has led to sufficient liver damage (approaching 50% of total liver volume) to result in decreased bilirubin excretion and jaundice
- Provides a visual assessment of imbalances between arms and number of cases by quadrants, also known as Evaluation of Drug-Induced Serious Hepatoxicity (eDISH)

Importance: hepatocellular jaundice due to DILI is considered Hy's Law cases, which can carry a 10% mortality risk

- Presence of even 1 or 2 cases may jeopardize drug approval or raise concerns for post-marketing safety

Hepatocellular Screening Plot Interpretation

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



Source: [include Applicant source, datasets and/or software tools used].
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2 x ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3 x ULN, and ALP <2 x ULN (note ALP values are not circled). All patients with at least one postbaseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal

- Each point represents one subject
- **X-axis**: maximum post-baseline transaminase (ALT or AST) as multiples of ULN
- **Y-axis**: maximum post-baseline total bilirubin (TB) as multiples of ULN
- **Note**: maximum post-baseline for transaminase and Total bilirubin may not occur at the same timepoint
- References lines
  - X-axis: 3 x ULN
  - Y-axis: 2 x ULN
- Divides into 4 quadrants: the left lower quadrant indicates the risk of severe DILI is low

Hepatocellular Screening Plot Interpretation

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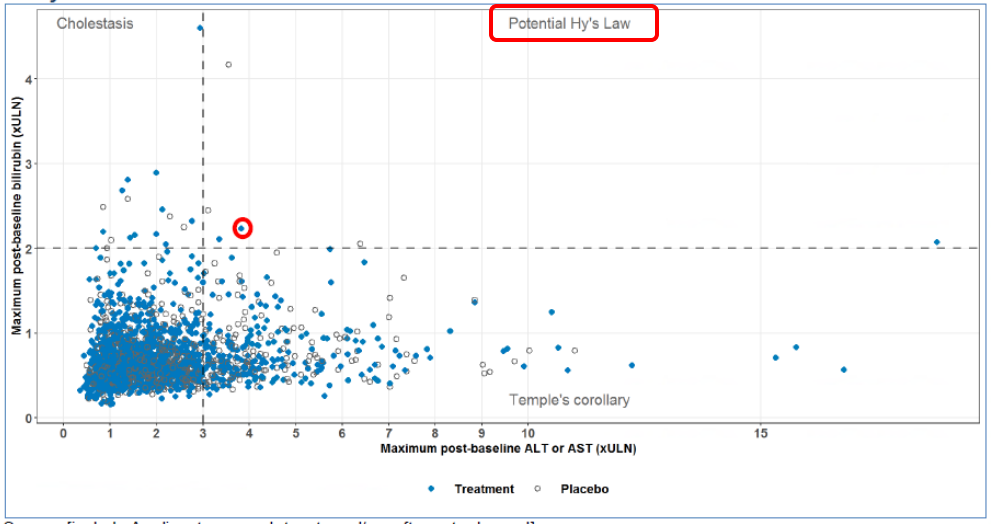

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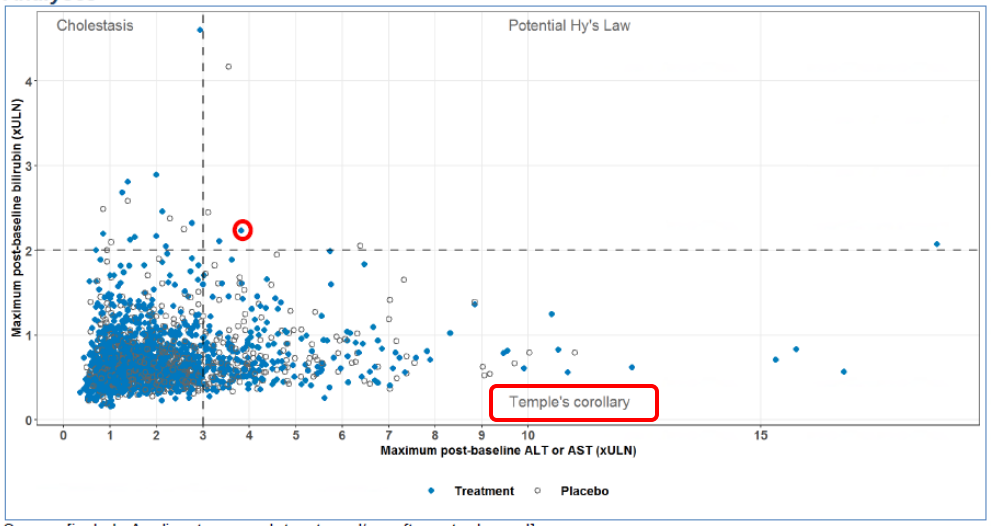
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal

Potential Hy's Law cases

- True Hy's Law criteria Identified by red circle
- **Predominant hepatocellular injury**: ALT/AST >=3 x ULN & TB >=2 x ULN, which represents sufficient loss of hepatic cells to interfere with bilirubin excretion
- TB elevation occurred within prespecified timeframe (eg, 30 days) after any post-baseline AST or ALT elevation >=3 x ULN
- **Absence of cholestaic injury**: indicated with a normal or only modestly elevated concurrent ALP level (< 2 x ULN)

Hepatocellular Screening Plot Interpretation

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



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Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
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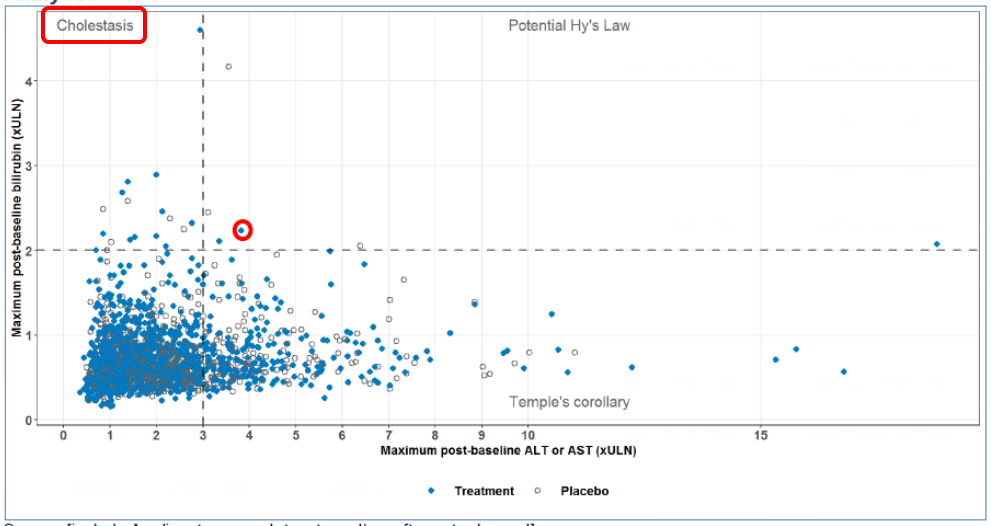
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal

Temple's Corollary

- ALT and/or AST >=3 x ULN & TB < 2 x ULN (no accompanying TB elevation or jaundice)
- Consider as potential DILI: subjects may have discontinued study drug due to transaminase elevations and did not progress to TB elevations meeting Hy's Law criteria

Hepatocellular Screening Plot Interpretation

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



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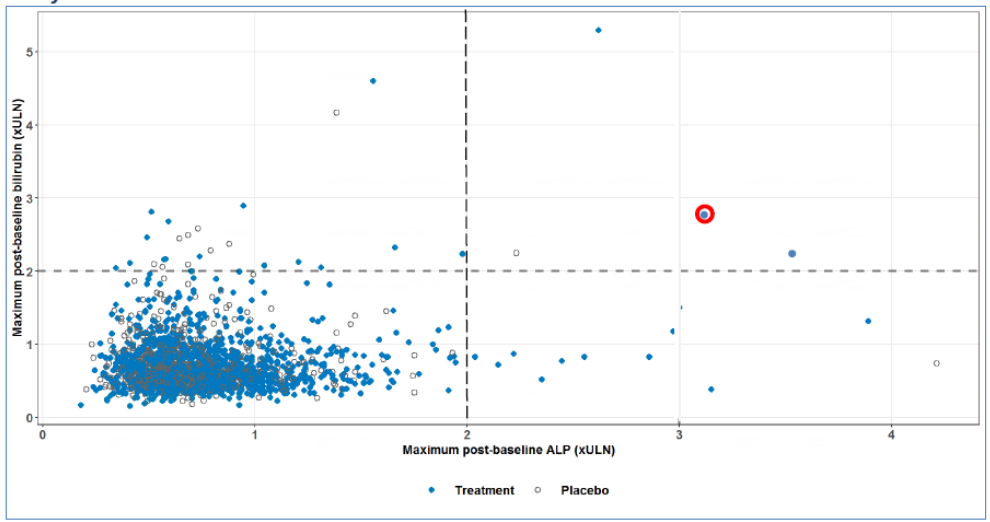
A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2 x ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3 x ULN, and ALP <2 x ULN (note ALP values are not circled). All patients with at least one postbaseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal

Cholestasis

- ALT and AST <3 x ULN & TB >= 2 x ULN (jaundice with no or minimal hepatocellular injury)
- Consider as potential significant DILI: certain drugs can be associated with predominant cholestatic injury that leads to an increased risk for serious liver adverse outcomes, e.g., vanishing bile duct syndrome

Cholestatic Screening Plot Interpretation

Figure 13. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



Source: [include Applicant source, datasets and/or software tools used].
Each data point represents a patient plotted by their maximum ALP versus their maximum total bilirubin values in the postbaseline period.
A potential cholestatic drug-induced liver injury case (red circled) was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2 x ULN within 30 days after postbaseline ALP became equal to or exceeding 2 x ULN.
Abbreviations: ALP, alkaline phosphatase; ULN, upper limit of normal

- Quickly identify significant ALP elevation in the setting of hepatic dysfunction (jaundice)
- The combination of ALP >= 2 x ULN and jaundice is concerning for cholestatic injury deserving exploration

- **X-axis**: maximum post-baseline ALP as multiples of ULN
- **Y-axis**: maximum post-baseline total bilirubin (TB) as multiples of ULN
- References lines for both axes: 2 x ULN

- Red circle: indicates subjects who had their maximum bilirubin within 30 days of ALP becoming > 2 x ULN

Maximal Trt. Emergent Liver Test Abnormalities

Purpose:

- Demonstrate potential imbalances in the proportion of patients who are found in each quadrant of concern between study arms using maximum treatment-emergent liver test abnormalities.
- Helps differentiate potential DILI cases in the active group vs. the comparator group

Table 29. Patients in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses

Quadrant	Drug Name N = XXX n (%)	Placebo N = XXX n (%)
Potential Hy's Law (right upper)		
Cholestasis (left upper)		
Temple's corollary (right lower)		
Total		

Source: [include Applicant source, datasets and/or software tools used]
Abbreviations: N, number of patients in treatment arm; n, number of patients meeting criteria

Maximal Trt. Emergent Liver Test Abnormalities

- A similar table can be generated for the **cholestatic** liver injury screening plot if there is concern

Table 30. Patients in Each Quadrant for Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses

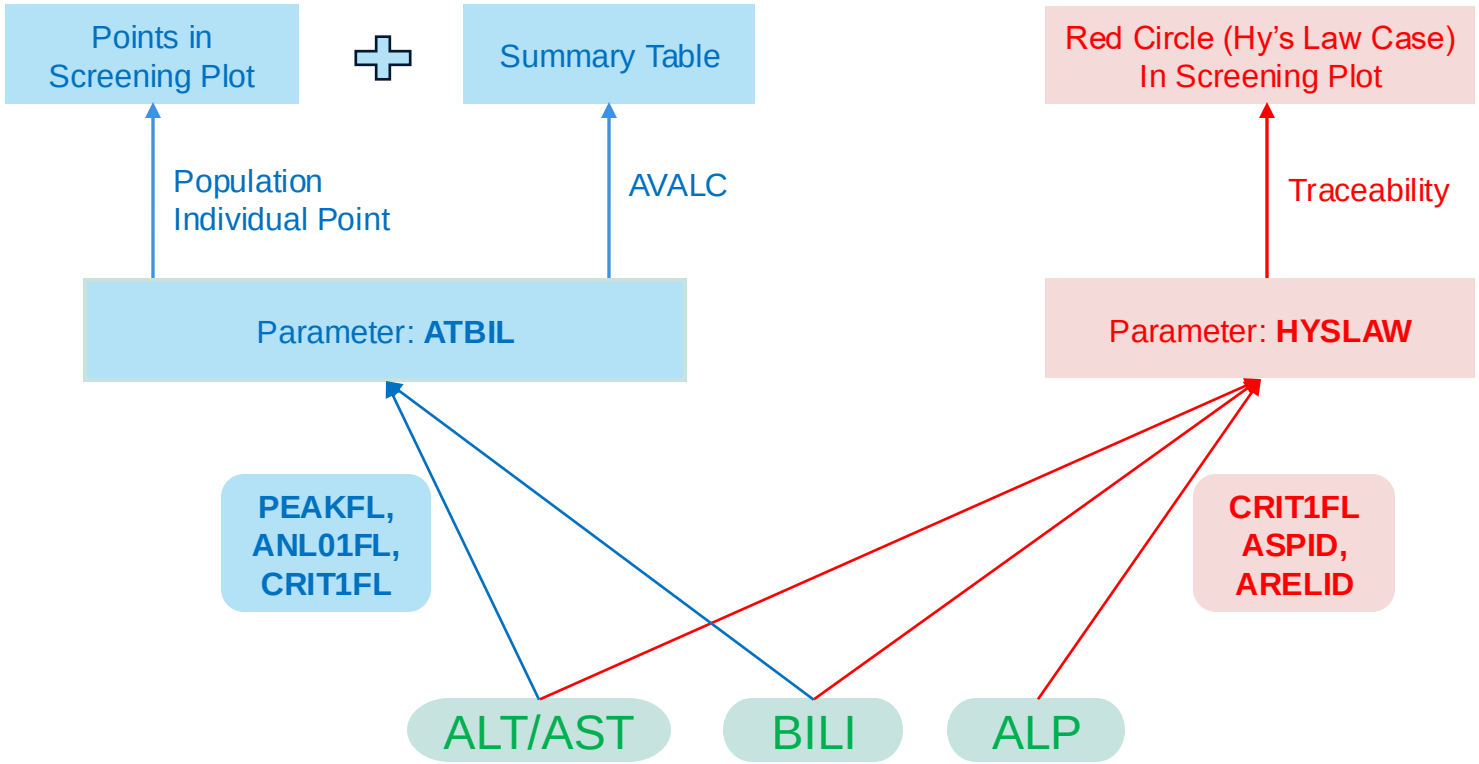
Quadrant	Drug Name N = XXX n (%)	Placebo N = XXX n (%)
Bilirubin ≥2 x ULN and ALP ≥2 x ULN (right upper)		
Bilirubin ≥2 x ULN and ALP <2 x ULN (left upper)		
Bilirubin <2 x ULN and ALP ≥2 x ULN (right lower)		
Total		

Source: [include Applicant source, datasets and/or software tools used].

Abbreviations: ALP, alkaline phosphatase; N, number of patients in treatment arm; n, number of patients meeting criteria; ULN, upper limit of normal

ADDILI Data Structure

Data Design Overview



ADDILI Structure

Standard BDS Structure

Variable Level

Variables	Description/Purpose
PARAMCD	
PARCAT1	Groups ALT and AST
AVALC	Summary table values
R2ANRHI	X and Y axis values
CRIT1/CRIT1FL	Flag for thresholds, e.g., >= 3 x ULN
PEAKFL	Maximum post-baseline flag
ANL01FL	Analysis enabling flag (unique record)
ASPID	Source lab identifier
ARELID	Traceability for compound parameters

Value Level

Parameter Identifier	Description/Purpose
ALT	Source lab records
AST	Source lab records
BILI	Source lab records
ALP	Source lab records
ATBIL	Derived parameter for Hepatocellular screening plot
APBIL	Derived parameter for Cholestatic screening plot
HYSLAW	Derived parameter for Hy's Law cases
CHOLSTC	Derived parameter for Cholestasis cases

Source LB Derivations

USUBJID	ADT	PARAMCD	PARAMN	PARCAT1	R2ANRHI	CRIT1	CRIT1FL	PEAKFL	ANL01FL	ASPID
ABC-001	2022-06-20	ALT	1	Transaminase	21.566666667	>=3 x ULN	Y	Y		1-6
ABC-001	2022-06-20	ALT	1	Transaminase	21.566666667	>=3 x ULN	Y	Y		1-7
ABC-001	2022-06-20	ALT	1	Transaminase	21.566666667	>=3 x ULN	Y	Y	Y	1-8
ABC-001	2022-05-09	AST	2	Transaminase	1.2	>=3 x ULN	N			2-3
ABC-001	2022-05-30	AST	2	Transaminase	1.6	>=3 x ULN	N			2-4

- PARCAT1: Groups AST and ALT for derivations
- CRIT1FL: Cutoff (AVAL/ANRHI) met for each PARAMCD
- PEAKFL: Within USUBJID and PARCAT1, select the post-baseline record with the highest R2ANRHI
- ANL01FL: If multiple records selected by PEAKFL, pick unique one (e.g., with earliest date and largest LBSEQ)
- ASPID: Builds **traceability**, concatenating **PARAMN** + derived sequential number

Bridging Parameter: ATBIL

Purpose:

- **Analysis-ready** parameter for both screening plot and maximal abnormality table
- **One record per subject**, serves as the population for the plot and table

Logic:

- Selecting the maximum post-baseline ANRHI from 2 sources (X and Y axis):
  - **AST/ALT** (**PARCAT1** = Transaminase)
  - **BILI** (**PARCAT1** = Total Bilirubin)
- Combine 2 sources and assign the category (**AVALC**) based on **CRIT1FL**

USUBJID	ADT	PARAMCD	PARAMN	PARCAT1	R2ANRHI	CRIT1	CRIT1FL	PEAKFL	ANL01FL	ASPID
ABC-001	2022-06-20	ALT	1	Transaminase	21.566666667	>=3 x ULN	Y	Y	Y	1-8

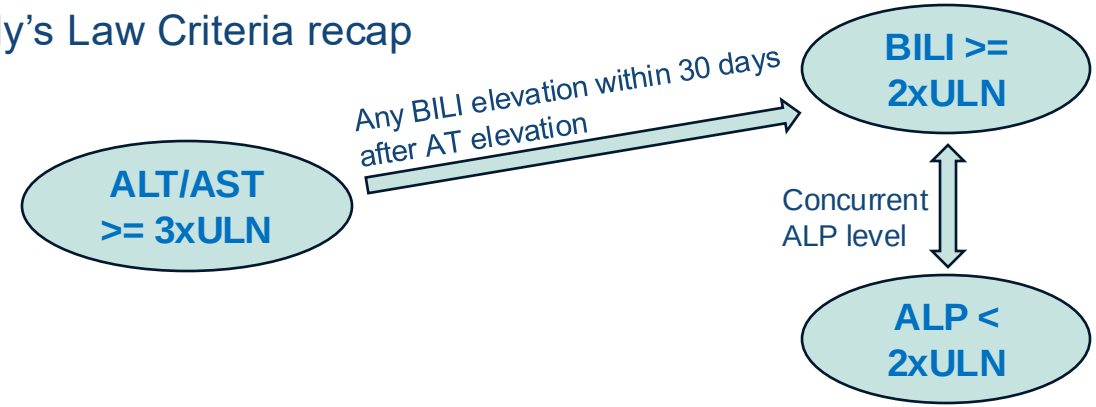
USUBJID	ADT	PARAMCD	PARAMN	PARCAT1	R2ANRHI	CRIT1	CRIT1FL	PEAKFL	ANL01FL	ASPID
ABC-001	2022-04-19	BILI	3	Total Bilirubin	1.0666666667	>=2 x ULN	N	Y	Y	3-2

Combine

USUBJID	PARAMCD	AVALC	ARELID
ABC-001	ATBIL	Temple's corollary (right lower)	1-8, 3-2

The Red Circle

- Hy's Law Criteria recap



NOTE: ANY post-baseline records, NOT just maximum post-baseline

- Multiple records per subject, using ARELID to build traceability

USUBJID	PARAMCD	AVALC	ANL01FL	ARELID
ABC-001	HYSLAW	Y	Y	2-6, 3-5, 4-6
ABC-001	HYSLAW	Y		2-6, 3-6, 4-6
ABC-001	HYSLAW	Y		2-6, 3-7, 4-6

AREID: concatenate ASPID of AT, BILI and ALP

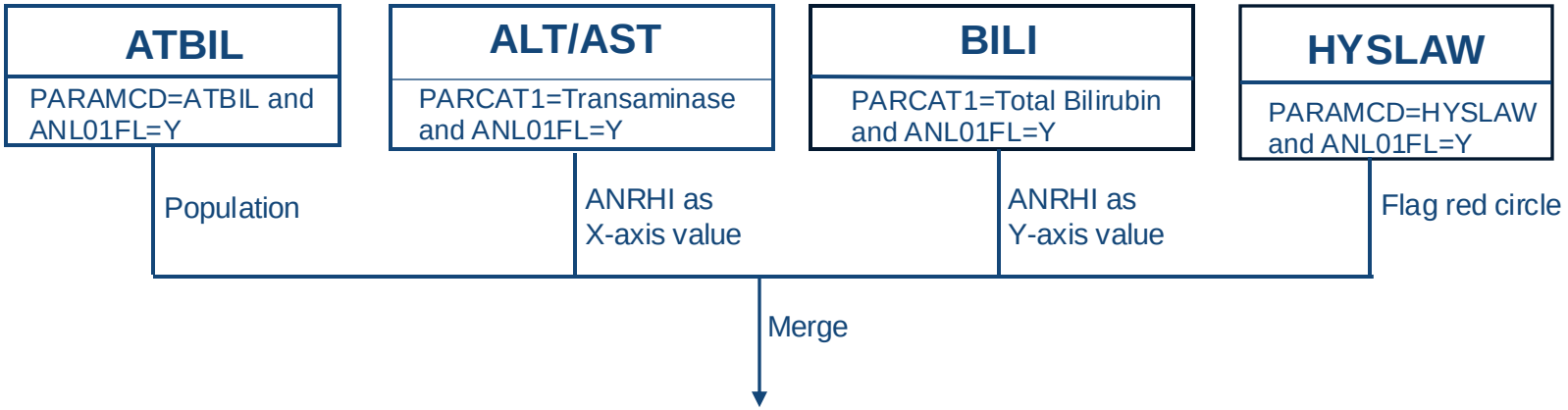
ANL01FL: flag one record for plot

Table & Figure Generation

- **Maximal Abnormalities Table**

  Use PARAMCD=**ATBIL** and do frequency count on AVALC

- **Screening Plot**



USUBJID	PARAMCD	AVALC	ATMAX	BLMAX	HYSFL
ABC-001	ATBIL	Potential Hy's Law (right upper)	6.3684210526	4.2608695652	Y

Summary

The proposed ADDILI follows standard BDS to streamline analyses

- Simplified derivations for post-baseline ALT and/or AST grouping by using PARCAT1
- Improved data completeness with PEAKFL showing all maximum post-baseline records
- Bridging table and figure generation using derived parameters ATBIL/APBIL
- New parameters HYSLAW and CHOLSTC to demonstrate data flow from source lab to Hy's Law or Cholestasis cases (compound criteria)
- Analysis ready flag ANL01FL to enable straightforward record selection for table and plot generation
- Enhanced traceability for compound parameters with ASPID & ARELID to show full data lineage

Acknowledgements

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Thank You!