PP20
PhUSE CSS White Paper on Analyses Associated With Hepatotoxicity

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WG5 Project 08: Introduction

Project Purpose:

• Create 6 white papers outlining recommended analyses for common Tables, Figures, and Listings (TFLs) for clinical trial study reports and integrated summary documents,

• Develop code created in the PhUSE wiki for the recommended TFLs.
WG5 Project 08: 6 White Paper Topics

1. Analyses and Displays Associated with Measures of Central Tendency – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Submission Documents

2. Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Submission Documents

3. Analyses and Displays Associated with Adverse Events and Deaths – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents

4. Analyses and Displays Associated with Demographics, Medications, and Disposition – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents

5. Analyses and Displays Associated with Hepatotoxicity – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents

6. Analyses and Displays Associated to Pharmacokinetics – with a focus on clinical trials
White Paper Status: Preliminary Draft

Analyses and Displays Associated with Hepatotoxicity – With a Focus on Phase 2-4 Clinical Trials and Integrated Submission Documents

Version 1.0
Created xx XXXX 201x

A White Paper by the PhUSE Computational Science Symposium Development of Standard Scripts for Analysis and Programming Working Group

This white paper does not necessarily reflect the opinion of the institutions of those who have contributed.
Overview of FDA Guidance: July 2009

• “Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation”


• Addresses how laboratory measurements that signal the potential for such drug-induced liver injury (DILI) can be obtained and evaluated during drug development

• Severe DILI is RARE: often <1 in 10,000
Hyman (Hy) Zimmerman, M.D. (1914-1999), a major scholar of DILI

**Hy’s Law:** Observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury.
Hy’s Law: 3 Components

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.

2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP).

3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.
Hy’s Law

- Proposed Figure for evaluation: Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH)

**Maximum Total Bilirubin vs. Maximum Alanine Aminotransferase**

- **Hyperbilirubinemia**
- **Hy’s Law Range**
- **Placebo (N = 1273)**
- **Drug (N = 1245)**

ULN = upper limit of normal of the reference range
Points do not necessarily represent values from the same blood draw.
Laboratory Elevations of Interest

Proposed tabular summaries, including graphs:

• 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST (AT)
• Any elevations of TBL to >2xULN
• Any elevations of ALP >1.5xULN
• Elevation of AT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN)

General Considerations:

• How to incorporate baseline value
• Whether to report P-values and Confidence Intervals
Adverse Events Analysis

Analysis of the following Standardized MedDRA Queries (SMQs) can to assess liver injury and function, and summarized by both broad and narrow terms. The MedDRA preferred terms should be nested within the SMQ.

– Broad and narrow terms in the liver related investigations, signs and symptoms SMQ (20000008)
– Broad and narrow terms in the cholestasis and jaundice of hepatic origin SMQ (20000009)
– Broad and narrow terms in the hepatitis non-infections SMQ (20000010)
– Broad and narrow terms in the hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013)
– Narrow terms in the liver-related coagulation and bleeding disturbances SMQ (20000015)
Adverse Events Analysis

Possible Table Layout, details to be determined.

<table>
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<th>Broad Definition</th>
<th>Treatment A (N=xxx)</th>
<th>Treatment B (N=xxx)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n_1 (xx.x)</td>
<td>n_2 (xx.x)</td>
</tr>
<tr>
<td>Narrow definition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred Term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects reporting treatment emergent adverse events</td>
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</tr>
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<td>Liver related investigations, signs and symptoms SMQ (20000008)</td>
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<td>Cholestasis and jaundice of hepatic origin SMQ (20000009)</td>
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<tr>
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</tr>
<tr>
<td>... and so on ...</td>
<td>xx (xx.x)</td>
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</tr>
</tbody>
</table>
Individual Display

- Patients for further interest summarized graphically, including:
  - Laboratory results vs ULN
  - Dosing start/stop day
  - Relevant Adverse event start/stop day
  - Dates of other important events (important medication start/stop days, transplantation date, etc.)
Individual Display

Possible Figure Layout, details to be determined.
Conclusions

• Draft 1 of the white paper is currently in preliminary draft form

• Next Steps include:
  – Collect feedback
  – Other displays for consideration
  – Maintain consistency with displays in other white papers

• This white paper provides guidance and foundation for the work in the Script-athon, for e-DISH plot.

• For further information, www.phusewiki.org

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