PhUSE Computational Science Symposium (CSS) White Paper on Analyses and Displays Associated with Adverse Events

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Introduction

- Industry standards have evolved for data collection (CDASH), observed data (SDTM), and analysis datasets (ADaM) leading to the recognized need for developing standard tables and figures for common assessments across clinical trials and across therapeutic areas.

- The PhUSE Development of Standard Scripts for Analysis and Programming Working Group is leading an effort to create several white papers providing recommended analyses and displays for common safety measurements, and has developed a Script Repository as a place to store shared code.

- The FDA Safety Reviewer Guidance includes discussion sections on safety review of deaths, other serious adverse events, dropouts and other significant adverse events, adverse events associated with dropouts, common adverse events, and also additional adverse event analyses and explorations.

- This poster will cover the recommended tables and figures associated with this safety review as outlined in the draft white paper titled "Analyses and Displays Associated with Adverse Events – Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Submission Documents".
**PhUSE CSS Working Group**

**WG 1: Data Validation and Quality Assessment**

**WG 2: Standardizing data within the Inspection Site Selection Process**

**WG 3: Challenges of Integrating and Converting Data across Studies**

**WG 4: Standards Implementation Issues with the CDISC Data Models**

**WG 5: Development of Standard Scripts for Analysis and Programming**

**WG 6: Non-Clinical Road-map and Impacts on Implementation**

**P01: Look for existing scripts and store them in the repository**

**P02: Define validation steps for scripts in the repository**

**P03: Establish platform (repository) for sharing scripts**

**P04: Legal ownership and issues in open source repository**

**P05: Create templates for documenting scripts**

**P06: Process for creating and editing scripts in Google Code**

**P07: Develop communication plan for standard scripts**

**P08: Create white papers providing recommended display and analysis including Table, List and Figure shells**

**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 – 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 Non-Compartmental Pharmacokinetics – with a focus on clinical trials**
1. Analyses and Displays Associated with Adverse Events – Focus on Adverse Events in 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.
Examples of Discussed Topics

• General Considerations
  – Which treatment comparison statistics to include: P-values, Percent Differences, Confidence Intervals, Odds Ratio, and/or Relative Risk
  – Whether or not to incorporate AE grades in tables
    • Eg., CTCAE grades 1-5, mild/moderate/severe
Recommended Tables, Figures

**Treatment Emergent Adverse Events in Descending Order of Preferred Term with Treatment Comparison Statistics**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Treatment A n (%)</th>
<th>Treatment B n (%)</th>
<th>Total n (%)</th>
<th>Comparison Statistics (TBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects reporting treatment emergent adverse events</td>
<td>xx (xx.x)</td>
<td>xx (xx.x)</td>
<td>xx (xx.x)</td>
<td>xx</td>
</tr>
<tr>
<td>Preferred term 1</td>
<td>xx (xx.x)</td>
<td>xx (xx.x)</td>
<td>xx (xx.x)</td>
<td>xx</td>
</tr>
<tr>
<td>Preferred term 2</td>
<td>xx (xx.x)</td>
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</tbody>
</table>

*Coded using MedDRA version xx*
### Treatment Emergent Adverse Events in Descending Order of Preferred Term within System Organ Class with Treatment Comparison Statistics

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Treatment A n (%)</th>
<th>Treatment B n (%)</th>
<th>Total n (%)</th>
<th>Comparison Statistics (TBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects reporting treatment emergent adverse events</td>
<td>xx (xx.x)</td>
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<tr>
<td>System Organ Class 1</td>
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<tr>
<td>Preferred term 1.1</td>
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<tr>
<td>System Organ Class 2</td>
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<tr>
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</table>
First 20 AEs that having highest risk in the Treated group comparing to Placebo group.

***, **, * statistically significant at 0.001, 0.01, and 0.05 level, respectively.

P-value from fisher's exact test.
Conclusion

• White Paper is currently in preliminary draft form
• Next Steps include:
  – Collect feedback
  – Other displays for consideration
• This white paper provides guidance and foundation for the work in the Script-a-thon.
Acknowledgements

• The authors would like to thank Karolyn Kracht, MS, for her assistance in the preparation of this poster
Further Information

www.phusewiki.org