PhUSE CSS White Paper on Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal

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INTRODUCTION

Industry standards have evolved over time for data collection (CDISC), observed data (ISTM), and analysis datasets (ADAM). There is now recognition that the next step would be to develop standard tables and figures for common measurements across clinical trials and across therapeutic areas. The development of standard scripts for analysis and programming WG is leading an effort to create several white papers providing recommended analyses and displays for common measurements, and has developed a script repository as a place to store shared code.

This poster will cover the recommended tables and figures associated with outliers or shifts from normal to abnormal, as outlined in a draft white paper titled “Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal – Focus on Vital Sign, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2 Clinical Trials and Integrated Submission Documents”. The FDA Safety Reviewers’ Guidance includes a statement that the safety review of laboratory data should include a review that focuses on patients whose values deviate substantially from a reference range. This white paper provides guidance and displays for ECGs and vital signs. In addition to the final recommendations, this poster will cover reasons for the recommendations and various alternatives that were considered. Developing shared code to create the displays in this white paper is planned for the script repository.

Examples of Discussed Topics

• General Considerations
  • Whether to report P-values and Confidence Intervals
  • Handling of
    • Measures collected in reflex manner, repeated measures, unplanned measures, measurements post drug exposure
    • Baseline definition Multi-phase Clinical Trials
  • Laboratory Analyte Measurements
  • Handling of central versus local laboratories
  • Choices of lab reference limits

Tables and Figures

Recommended for Quantitative Measures

• Lack of patient level information
  • Lack of patient baseline
  • Lack of magnitude of change from baseline

Recommended for Qualitative Measures

• Lack of information on patient level information
  • Lack of magnitude of shift

Why Outlier/Shift Analyses?

Reviewer Guidance

Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

For Labs, ECG and Vital Signs, while at times a potentially important effect may be revealed only in analyses looking at differences in mean change from baseline:

‘marked outliers are typically of greatest interest from a safety standpoint.’

The review should focus on patients whose laboratory values deviate substantially from the reference range.’

Want to Review the White Paper?

Visit PhUSE wiki at http://www.phusewiki.org/wiki/index.php?title=WG5_Project_08

Conclusion

• Draft 1 of the white paper is currently under review.
  • We are collecting feedback
  • We also included in the white paper other displays that have been considered.
  • This white paper provides guidance and foundation for the work in the Scriptathon.