A Central Laboratory Inter-laboratory Comparison Program to Assess the Comparability of Data of Forty-one Tests from Four Regional Laboratories Involved in Global Clinical Trials over a Twelve-Month Period

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ABSTRACT

Objective
The objective of this study was to develop and support a process for assessing the comparability of data used in global clinical trials from four different laboratories, owned by the same central laboratory entity, and that the same tests on the same samples would be under statistical control and acceptable limits of variation.

Reference
Data from central laboratories have been key for assessing safety, tolerability, and efficacy of new drugs in clinical trials. With the increasing complexity and global scale of many clinical trials, it is important to maintain harmonization among the regional laboratories as part of a central laboratory participating in the same study. However, continuous monitoring of the same samples run at all laboratory locations may not be common practice.

Methodology
Pooled serum, plasma, and urine samples were aliquoted, frozen at -70°C, and distributed quarterly to each laboratory. Samples were analyzed weekly on the same day at each laboratory for twelve months. The percent and absolute bias were calculated for each result using the US laboratory as the reference laboratory. The percent bias for each week and month was also calculated. A Bland-Altman plot was created between each laboratory and the reference laboratory for the twelve-month period, and a student T-test was run using a relative bias limit for each test and a significance level of 5%.

Results
Overall, during the twelve month period, all forty-one tests had a twelve month mean bias within the acceptable bias limit for each individual test compared to the reference laboratory. When comparing the mean weekly bias from all laboratories, any week where the bias was outside acceptable limits, investigation and corrective action was undertaken to determine the source of the error. Examples include:

- One week during the six-month period, three chemistry tests from the same laboratory had a mean weekly bias outside the acceptable limits. After investigation, it was determined that a pre-analytical issue with thawing/mixing of frozen samples was the cause of the bias.
- A negative bias was observed in a US laboratory for triglyceride. However, subsequent review of CDC Lipid Standardization Program Part III data from all laboratories globally demonstrated acceptable performance.
- Inconsistencies in the reporting of results across laboratories, specifically the technical decision to report data deemed biologically implausible, were noted after monthly review of calcium data, and all technologists were re-educated on handling repeat analysis and appropriate consultation of Laboratory Directors.

Conclusion
An inter-laboratory program where frequent monitoring of identical samples run at all laboratories involved in clinical trials can provide valuable information into the harmonization of data reported by the central laboratory and help mitigate pre-analytic, analytic, and post-analytic issues that may arise when assessing data used in the development of new therapeutics.

INTRODUCTION

Data from central laboratories are key for assessing safety, tolerability, and efficacy of new drugs in clinical trials. The Inter-laboratory Comparison Program was set up among all laboratories wholly owned by Medpace Reference Laboratories (MLRL), a global central laboratory, in 2006. The locations include Cincinnati, OH (US), Leuven, Belgium (BE); Singapore (SG); and Beijing, China (CN). The program involves multiple platforms to assess over 40 analytes tested globally, encompassing several special laboratory areas including Oncology, Cardiometabolic, Infectious disease, and others.

Continuous monitoring of sample analysis at all regional laboratories is essential to ensure data harmonization within pre-defined acceptance criteria is maintained, irrespective of laboratory location.

METHODOLOGY

Samples
Pooled serum, plasma, and urine samples were aliquoted, labeled with the appropriate sample information, frozen at -70°C, and distributed quarterly to each laboratory for weekly analyses on the same day.

The pooled samples were from participants in clinical trials. All samples were received de-identified of demographic information.

Analytical methods
Over a 12-month period, sample analysis was performed on 41 tests (Table 1) at each Medpace laboratory location on weekly batches of 10 samples and were analyzed on the same day in each laboratory (N=520).

On the day of analysis, samples were thawed and thoroughly mixed.

Quality Control Tests were analyzed with each batch and results represented in acceptable limits of variation.

Acceptable results were electronically transferred into ClinTrak Lab®, an in-house, developed clinical trial management system.

RESULTS

All tests run on Beckman Coulter AU Series Chemistry Analyzers, Roche Immunoanalyzers, Siemens BNII Nephelometers, Stago Compact Coagulation Analyzers, Tosoh G7G8 HPLC Analyzers, or by preparative ultracentrifugation, demonstrated acceptable equivalence when compared to the reference laboratory for the 12-month period (Figure 1).

Some test and laboratory locations have an N of <520 for a given analyte and acceptable limits of variation.

Statistical methods
- Significance testing of the bias criteria, number of samples, and mean difference (absolute or relative) compared to the reference laboratory (USNL-USL) were included. The P-values are from TOST T-test performed on absolute or relative difference.

- A Bland-Altman plot was created between each laboratory and reference laboratory for the 12-month period (Figure 1).

Bias criteria were based on criteria from the College of American Pathologists, Westgard Biological Variation Database, and Royal College of Pathologists of Australasia.

Some tests and laboratory locations have an N of <520 for a given analyte due to insufficient quantity, instrument error, etc.

CONCLUSION

An inter-laboratory comparison program where frequent and continuous monitoring of identical samples analyzed at all laboratories involved in clinical trials is conducted can provide valuable information into the harmonization of data reported by the central laboratory and help mitigate pre-analytic, analytic, and post-analytic issues that may arise when assessing data used in the development of new therapeutics.

REFERENCES

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