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Clinical Validation of the ProTime InRhythm PT/INR in Professional Use Settings

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Introduction: The ProTime InRhythm™ (InRhythm) System is a point-of care device for the quantitative measurement of PT/INR in fresh whole blood from patients treated with oral Vitamin K Antagonists (VKA) therapy. The InRhythm System consists of an instrument and disposable cuvettes. Each cuvette consists of two PT microchannels containing human recombinant thromboplastin to analyze a patient's sample in duplicate to ensure accurate results, and a third internal control channel that is activated each time a test is performed to verify the integrity of the reagents and proper test procedure. The duplicate PT test results must agree within a specified limit in order for the test result to be displayed and stored. Each lot of thromboplastin used in the cuvettes is calibrated following WHO standard. The assigned MNPT and ISI are coded in the barcode of the cuvettes for each lot of PT reagents.

Objective: The objective of this non-randomized prospective multicenter clinical trial was to evaluate the accuracy of the InRhythm INR measurements in fingerstick (FS) and fresh venous whole blood (VWB) samples from patients receiving oral VKA therapy relative to plasma based reference laboratory method.

Methods: The study was executed at three clinical sites and testing was performed by 3 healthcare professional operators at each site. The study protocol and the informed consent were approved by the local Institutional Review Board at each center. Each site enrolled a minimum of 135 VKA patients at different INR therapeutic ranges and 15 healthy donors following established inclusion and exclusion criteria. Duplicate FS and VWB samples were collected and subsequently tested on multiple InRhythm instruments using three lots of cuvette equally distributed across the sites. Paired post-frozen citrated plasma samples were analyzed for INR measurements with the reference laboratory at Detroit Medical Center University Laboratories, Detroit, MI, using Dade® Innovin reagent and Sysmex® CA-1500 instrument (Siemens Healthcare Diagnostics Inc).

Results: A total of 455 subjects completed the study. Mean age VKA patients was 69.1 ± 11.4 yrs (22 – 94) including 68.3% males, average weakly dose was 40.3 ± 27.0 mg (6.0 – 410) and duration of therapy was 6.2 ± 5.4 yrs (0.2 – 42.3). Comparison of FS and VWB from the same donor showed no difference between the two sample types (r= 0.98, slope y= 0.99 (95% CI: 0.95 – 1.01), intercept= x -0.01 (95% CI: 0.01 – 0.16). Reproducibility of duplicate FS and VWB samples from the same donor was analyzed at different INR ranges (0.80 to > 4.5). Estimate of imprecision of duplicate samples evaluated at 6 INR levels yielded a %CV of 3% to 5% suggesting reproducibility performance of $\leq$5%. Both FS and VWB samples correlated well with the laboratory Innovin/Sysmex system using linear regression and weighted Deming analyses on 446 paired samples; e.g. linear regression analysis of FS was r= 0.93, slope= 1.0 (95% CI: 0.97 – 1.04) and intercept= -0.03 (95% CI: -0.14 – 0.07). Similar results were observed with Deming analysis. In the therapeutic range (>2.5 – 3.5 INR), there was 94.3% clinical agreement based on recognized standards. This level of agreement was observed across all sites participating in this study. In the aggregate (INR range: 0.90 to 8.9), total clinical agreement of 91.7% was observed which compares well with point of care expectations.

Conclusion: This study demonstrates that the InRhythm System, in the hands of professional users, is safe and effective in monitoring VKA therapy.