

VERIFICATION OF POCT-INR SYSTEM ACCURACY - A RETROSPECTIVE ANALYSIS OF PROTIME DATA USING THE PROPOSED ISO ACCURACY CRITERIA FOR SELF-TESTING OF ORAL ANTICOAGULANT THERAPY

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INTRODUCTION

Patient self-testing (PST) for anticoagulation management, using point-of-care (POC) INR devices has become a world-wide accepted methodology. In the effort to improve Time In therapeutic Range (TIR), there are clear advantages to increased test frequency and PST affords patients an increased access to INR testing.

With increasing use of PST, the international standards community, under the authority of the ISO TC 212 Committee, has instituted an initiative to provide INR system requirements for accuracy and precision. This proposed standard for PST devices, the ISO/CD 17593 document draft, is currently available for review and comment (access may be gained through www.CLSI.org). Among many proposed standards, the draft includes criteria for system accuracy when comparing the POCT-INR system against a reference laboratory INR standard.

ISO TC 212 **ISO/DIS 17593**
Clinical laboratory testing and in vitro diagnostic test systems —
Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy

Note: The ISO document is a Draft International Standard, circulated for comment and is copyright-protected by ISO.

ISO/CD 17593 GENERAL PROPOSED STANDARDS

- Design and Development Criteria
 - Risk Management Considerations
 - Quality Management Controls
 - Traceability
- Instructions for Use
- Safety and Reliability Testing
- Training and Education Programs
- System Performance Verification
 - Precision
 - Accuracy
- User Performance Evaluation

ISO CLINICAL VERIFICATION PROTOCOL REQUIREMENTS

- 3 study centers
- Combined Data
 - 20 normal donors
 - 180 patient (on oral anticoagulation) specimens

Distribution of INR Values of Samples for System Accuracy Verification

Number fraction of samples*	INR values
10 to 15 %	Below 2,0
15 to 40 %	2,0 to 2,8
15 to 40 %	2,9 to 3,7
10 to 30 %	3,8 to 4,5
5 to 10 %	4,6 to 6,0

ISO PERFORMANCE ACCEPTANCE CRITERIA

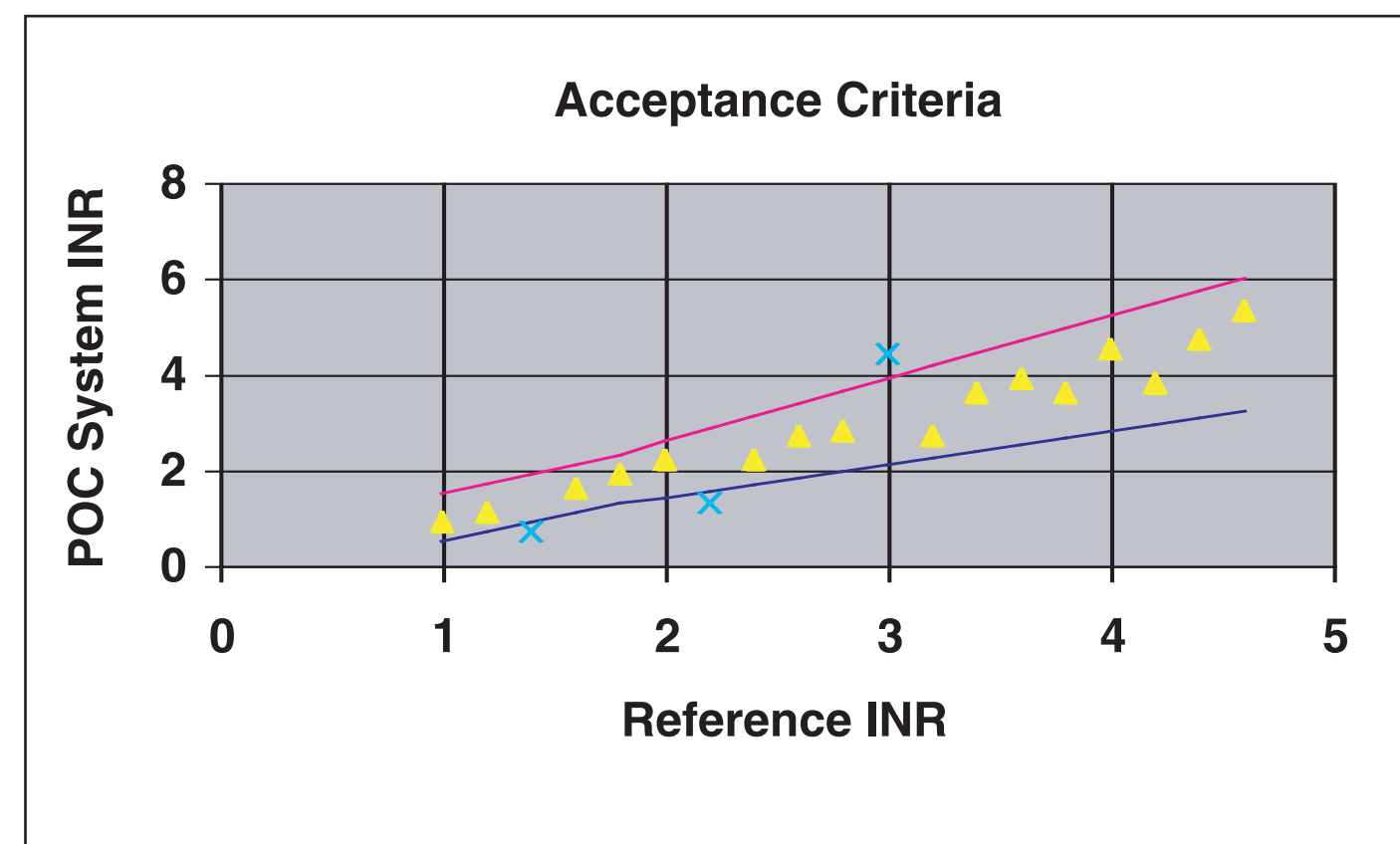
INR Interval	Allowable difference (90 % of results)	Allowable bias (average difference)
Below 2,0	± 0,5	NA
2,0 to 4,5	± 30%	± 0,3
4,6 to 6,0	NA	NA

NOTE 1: The minimum acceptable accuracy criteria are based on the medical requirements for oral-anticoagulation monitoring.

NOTE 2: Although no performance criteria are listed for INR values in the interval of 4,6 to 6,0, the difference and bias should be calculated and reported.

NOTE 3: The criteria apply to system accuracy verification studies in which professional system operators have received proper training, the device has been properly maintained and required adjustment and control procedures have been followed in accordance with the manufacturer's instructions for use.

ISO GUIDELINES FOR AGREEMENT



METHOD OF DATA SURVEY AND ANALYSIS

A review of published literature related to the ProTime Microcoagulation System, was conducted and the available clinical comparison data compiled and analyzed against the proposed ISO/CD 17593 guidelines.

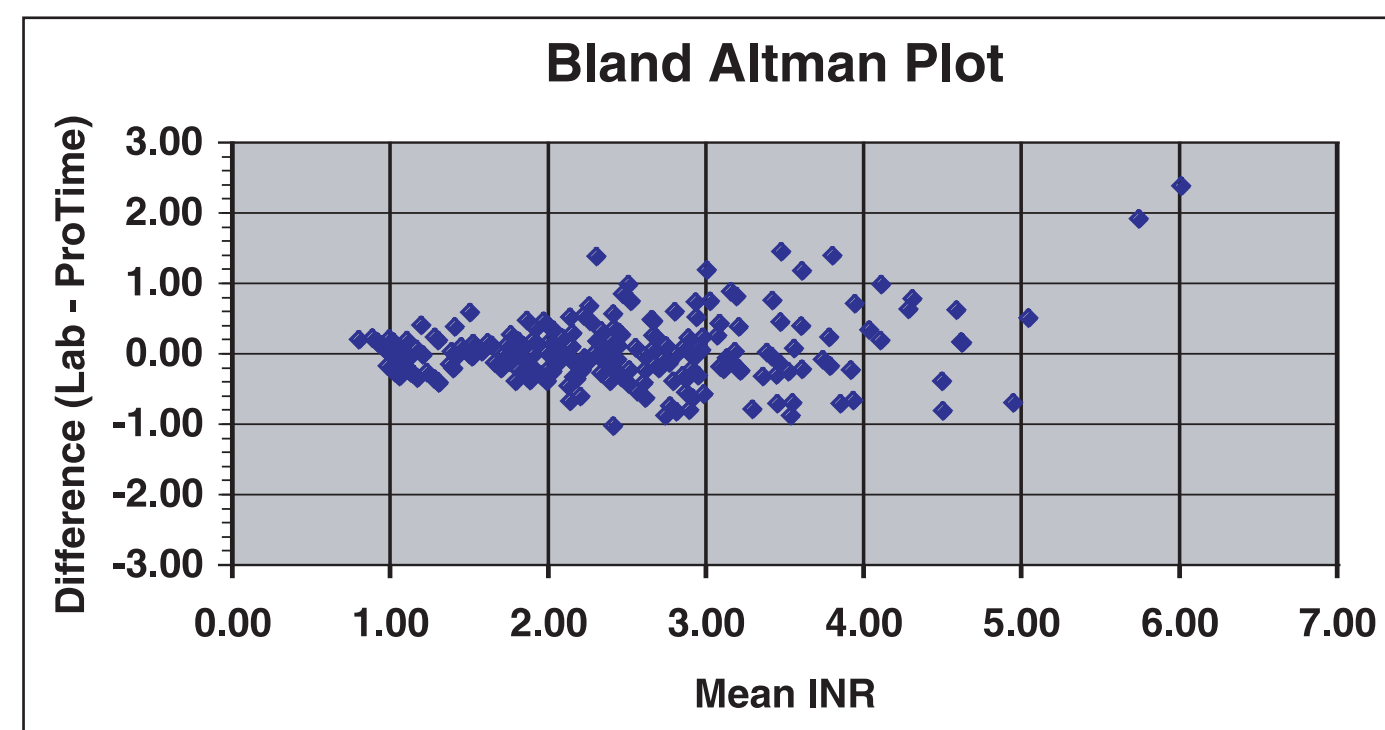
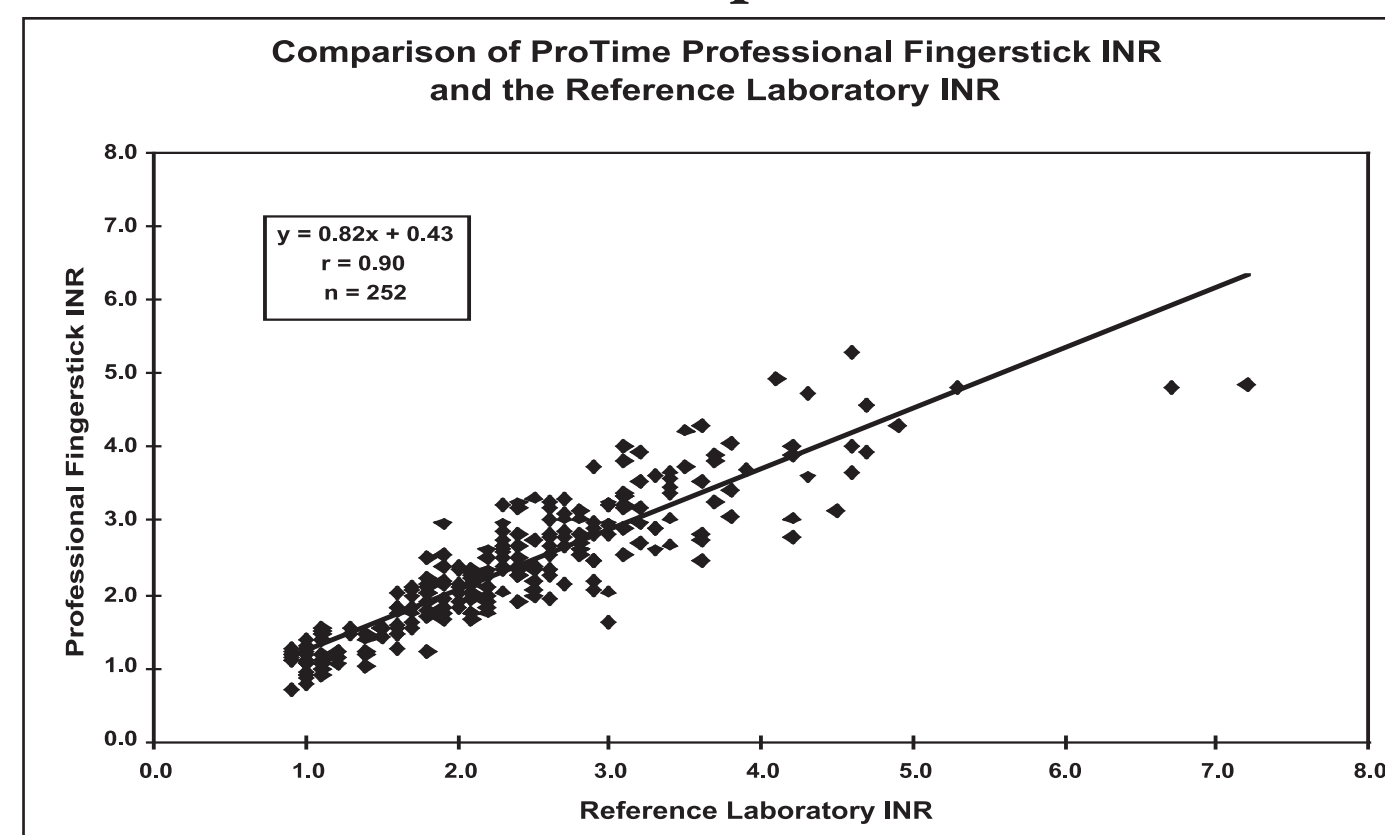
DATA AVAILABLE FOR ANALYSIS

- Seven published reference studies (see reference listing)
- 2467 paired INR results available
- INR range of 0.8 to 7.9 cited
- Raw data was available for analysis from 5 studies (2290 data pairs)
- Data survey and analysis
 - Agreement of paired results within 0.5 INR for INR range <2.0
 - Agreement within 30% for INR range 2.0-4.5
 - Summarized published clinical agreement

MATRIX OF COMPARATIVE LABORATORY INR SYSTEMS SURVEYED

Literature Reference	POC device	Blood Specimen (operator)	Lab Reagent	Lab Instrument	Data Set
Ref 1	ProTime	venous (professional)	Ortho Recomboplastin ISI = 1.0	MLA Electra 900	264 paired results data range = 0.8 to 6.8
Ref 1	ProTime standard	fingerstick (professional)	Ortho Recomboplastin ISI = 1.0	MLA Electra 900	252 paired results data range = 0.8 to 7.2
Ref 2	ProTime standard	fingerstick (self-test)	Ortho Recomboplastin ISI = 1.0	MLA Electra 900	407 paired results data range = 0.8 to 7.9
Ref 2	ProTime standard	fingerstick (professional)	Ortho Recomboplastin ISI = 1.0	MLA Electra 900	411 paired results data range = 1.0 to 6.9
Ref 3	ProTime standard	fingerstick (professional)	Organon Teknika ISI = 1.85	Sysmex CA1000	114 paired results
Ref 4	ProTime standard	fingerstick (professional)	Dade Innovin ISI=1.0	MLA Electra 900	228 paired results data range = 0.8 to 6.2
Ref 4	ProTime low volume	fingerstick (professional)	Dade Innovin ISI=1.0	MLA Electra 900	228 paired results data range = 0.8 to 6.2
Ref 5,6	ProTime standard	fingerstick and venous (professional)	Innovin recomoboplastin Innovin recomoboplastin	MLA BCS STA STA	100 paired results 100 paired results 100 paired results 100 paired results data range = 0.8 to 6.8
Ref 7	ProTime low volume	venous (professional)	rTF95 (WHO)	till-tube	63 paired results

Traditional Comparative Studies



Analysis of ProTime Clinical Agreement with ISO Guidelines

Literature Reference	Reported Clinical Agreement vs Lab		Applied ISO criteria **	
	Parameter	Value	Reported or Calculated	% agreement
Ref 1	INR agree within 0.4	77.3%	Calculated (from raw data)	93.4%
	INR agree within 0.7	93.6%		
Ref 1	not reported		Calculated (from raw data)	95.7%
				93.2%
Ref 2	not reported		Calculated (from raw data)	86.9%
				92.3%
Ref 2	not reported		Calculated (from raw data)	91.6%
				97.0%
Ref 3	Both in Therapeutic Range	56.3%	Not Available	
	Both below Range	28.3%		
Ref 4	INR agree within 0.4	79.0%	Calculated (from raw data)	90.4%
	INR agree within 0.7	94.3%		
Ref 4	INR agree within 0.4	83.3%	Calculated (from raw data)	95.6%
	INR agree within 0.7	95.3%		
Ref 5,6	INR agree within 0.4	74.7%	Calculated (from raw data)	97.4%
	lowest agreement	89.9%		
Ref 5,6	INR agree within 0.7	87.9%		98.1%
	lowest agreement	99.0%		
Ref 7	pairs within 0.5 INR of mean	90.0%	Not Available	
	Both in Therapeutic Range	67.0%		
Ref 7	Both above or below Range	19.0%		
	Diff of pairs <10% of avg	60.0%		
Ref 7	Overall Agreement	89.0%		

The percent agreement of the ProTime to the lab (5 different lab systems) ranged from 86.9 - 97.4% (<2.0 INR) and 92.3 - 98.1% (2.0-4.5 INR). These ISO criteria agreements were comparable to the clinical agreement limits originally published in the citations which evaluated the percentage agreement of pairs within 0.4, 0.7 and 1.0 INR over the entire INR range, namely 75-84% agreement at 0.4 limit, 88-99% agreement at 0.7 and >96% (1.0 limit). For two studies in which agreement was categorized by therapeutic range agreement (89% total agreement) and values within 0.5 INR (87 - 90% agreement), raw data was not available for ISO criteria comparison.

Presentation of Results for Lay (Patient) Users

INR interval (Acceptance criteria)	% of acceptable results
Below 2.0 (Within +/- 0,5 INR)	93%
2.0 to 4.5 (Within 30%)	95%

ASSESSING IMPACT ON CLINICAL INTERVENTION – THE ISO COMMITTEE PERSPECTIVE

The agreement analysis is designed to model the degree to which INR differences among POC (for PST) and lab systems may influence the management of oral anticoagulation. Surveying conventional clinical tools it was observed that correlation analysis commonly employ a mean versus difference analyses to determine when paired data could elicit different clinical response. Numerous studies have employed a number of analytical parameters, such as the percentage of values with INR differences of 0.4, 0.7 and 1.0 INR. Other studies have employed a 2 x 2 matrix assessing the percentage of paired results agreement within therapeutic range and out of therapeutic range and thus doing a modified "false negative" and "false positive" analysis. In the later the concept of patient treatment being directed by an Expanded Therapeutic Range has been adapted in several clinical centers, thus avoiding excessive dose changes to small INR changes which may have the undesired impact of causing erratic INRs. Upon reviewing all published options the committee elected to use the percentage agreement approach as described herein using a two tiered system, i.e., < 2.0 INR and 2.0 - 4.5 INR. Recognizing the inherent variability of INR values of 4.5 and above, the committee agreed to not set requirements for these values, though encouraged publications by the manufacturer if the data was available. Data above an INR of 6.0 was deemed too variable, due to INR system influence to yield meaningful comparison.

CONCLUSION

The ISO/CD document draft requires specific data collection and INR agreement for verification of proposed PST system devices. A retrospective review of ProTime data, which is within the recommendation limits demonstrates the applicability of the proposed INR agreement requirements, acknowledging that these trials were not collected using the INR sample distribution requirements of the proposed standard.

CITED STUDY REFERENCES

1. Oral Anticoagulation Monitoring Study Group - Point of care prothrombin time measurement for professional and patient self-testing use. (Group consists of - M Andrew, J Ansell, D Becker, R Becker, D Triplett Am J Clin Path 115:288-296, 2001
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