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2nd Edition

POCT14

Point-of-Care Coagulation Testing and Anticoagulation Monitoring

This guideline provides recommendations to users and manufacturers of point-of-care coagulation testing devices for monitoring heparin and vitamin K antagonist therapy and for the evaluation of hemostasis, as well as to ensure reliable results comparable with those obtained by routine medical laboratory testing.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

Point-of-Care Coagulation Testing and Anticoagulation Monitoring

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Abstract

Clinical and Laboratory Standards Institute guideline POCT14—*Point-of-Care Coagulation Testing and Anticoagulation Monitoring* provides consensus recommendations regarding quality indicators and performance standards for diagnostic coagulation examinations performed in near-patient settings. Point-of-care coagulation testing has evolved to include multiple assays based on traditional laboratory examinations. As with other noncoagulation point-of-care testing (POCT), “near-patient” or “bedside” testing provides examination results more rapidly than can be achieved in hospital or reference laboratory settings. This availability is important in intensive care units, emergency departments, operating rooms, and outpatient clinics, in which immediate diagnostic information may help expedite treatment decisions and positively influence patient compliance with therapy. This guideline provides a composite of applications of coagulation testing and anticoagulation management currently available. It includes performance requirements and clinical applications for point-of-care prothrombin time/international normalized ratio for vitamin K antagonist therapy (ie, oral anticoagulation therapy), as well as activated partial thromboplastin time and activated clotting time to monitor heparin therapy. Precision and accuracy compared with reference methods and clinical anticoagulation targets are presented for specific clinical applications of each type of examination. This guideline also covers the use of these assays for assessing hemostasis, an application that has been underused in POCT to date. POCT14 provides guidance for producing reliable and clinically useful examination results for any POCT setting or personnel.

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Foreword

Portable devices capable of producing immediate results at the point of care continue to evolve to meet the demands of the medical community. Acceptance of clinical coagulation testing traditionally performed by and under the supervision of trained laboratory professionals now being performed by personnel not trained in medical laboratory practice or by patients/caregivers in the home continues to be a challenge. However, it is the responsibility of device manufacturers to provide test systems capable of delivering accurate results when used by the intended operator as instructed by the device manufacturer. Professionals in laboratory medicine should support high-quality point-of-care coagulation testing (POC-CT) services. POC-CT has been and will continue to be implemented in different sites in a health care facility, such as the catheterization laboratory, operating room, emergency department, intensive care unit, postsurgical recovery room, hemodialysis unit, ambulatory care site, and clinical trial investigation sites. Outside of the hospital setting, limited POC-CT is performed by patients or by their caregivers in the patient's home. The selection of patients for self-testing is the responsibility of the treating health care provider.

POCT14 provides manufacturers with information on how to develop POC-CT systems for optimal performance. It provides users with information on how to evaluate, implement, and monitor POC-CT. This guideline assumes that implementation of POC-CT is under the supervision of a medical laboratory. The format is designed to be easy to follow for users who do not have expertise in hematology.

Overview of Changes

This guideline replaces the previous edition of the approved guideline, POCT14-A, published in 2004. Several changes were made in this edition, including:

- Added assay-specific performance criteria for both manufacturers and end users
- Provided recommendations for performance criteria for the use of POC-CT in the evaluation of patients with suspected bleeding disorders

NOTE: The content of this guideline is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

Key Words

Activated clotting time, activated partial thromboplastin time, coagulation, international normalized ratio, point of care, prothrombin time

Point-of-Care Coagulation Testing and Anticoagulation Monitoring

Chapter 1: Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Background information pertinent to the guideline's content
- Standard precautions information
- Terminology information, including:
 - Terms and definitions used in the guideline
 - Abbreviations and acronyms used in the guideline

1.1 Scope

This guideline provides recommendations for establishing and/or assessing performance characteristics of traditional assays for coagulation assessment and anticoagulation management that are performed at the point of care (POC). These tests include those used for monitoring vitamin K antagonists (VKAs) (eg, prothrombin time/international normalized ratio [PT/INR]) and heparin (eg, activated partial thromboplastin time [APTT], activated clotting time [ACT], and heparin concentration). POCT14 also includes recommendations for use of point-of-care testing (POCT) when APTT and PT/INR are used to evaluate individuals for suspected coagulopathies before or after invasive procedures or in association with the administration of certain pharmaceutical agents. This guideline provides minimal reference to the use of point-of-care coagulation testing (POC-CT) for monitoring direct thrombin inhibitors (DTIs). Potential assay interferences, including direct oral anticoagulants (DOACs), are briefly discussed.

The intended users of this guideline are manufacturers, regulatory organizations, and health care professionals. Recommendations are provided on how to assess accuracy and precision of traditional coagulation assays, as well as how to assess clinical safety and effectiveness. This guideline does not cover other hemostasis assays such as viscoelastic tests, either thromboelastometry or thromboelastography, or POC platelet function tests.

1.2 Background

Most POC-CT systems use whole-blood specimens. Test systems vary with regard to specimen volume requirements, active reagents, and end-point detection methods but have in common single-use cartridges or test strips, which are discarded after testing. In addition to providing immediate test results and decreasing the need for venipuncture, POC-CT enables more frequent assessment of hemostasis and coagulopathy. Clinicians value the decrease in turnaround time, which leads to faster decisions, improved clinical outcomes, and reduced length of stay.¹ In critical

care units and the emergency department, POC-CT is used to evaluate the effectiveness of drug therapy and to assess unexplained bleeding.

POC-CT devices have also been an integral component of global clinical trials for pharmaceutical companies developing novel anticoagulant drugs. POCT results, including POC-CT, trigger an immediate medical decision, and testing is most often performed by individuals with limited or no laboratory expertise. CLSI documents POCT04,² POCT07,³ and POCT09⁴ offer specific recommendations to ensure that POCT devices of all types produce reliable, clinically useful results. These documents also discuss risk assessment and quality management of POCT devices.

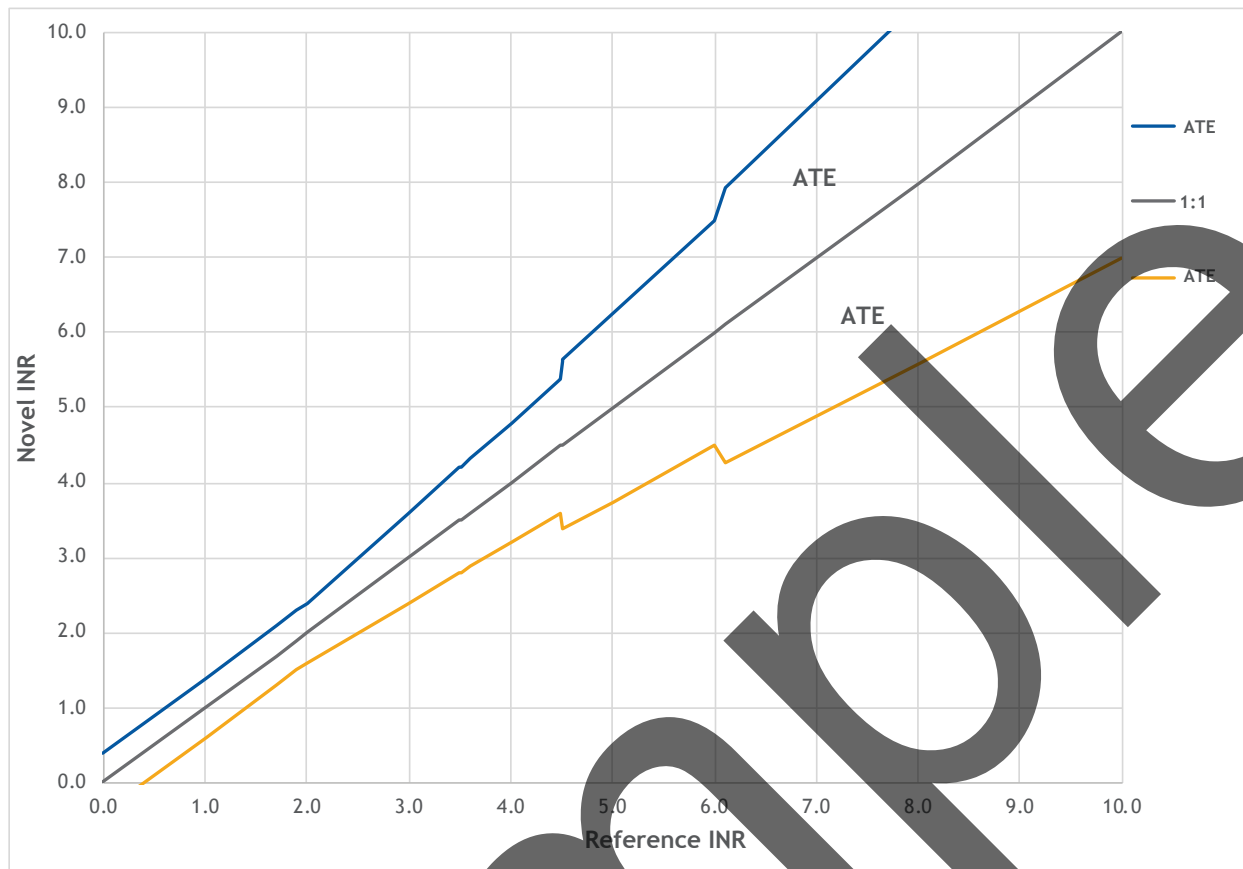
1.2.1 Point-of-Care Monitoring of Vitamin K Antagonist Therapy

VKA therapy has traditionally been monitored using PT performed in laboratories. Laboratory-based PT combines thromboplastin, calcium chloride, and citrated plasma. PT measures both the extrinsic coagulation pathway and the common coagulation pathway and is sensitive to vitamin K-dependent factors (II, VII, X). The original Quick PT is one of the first universal coagulation tests. The results of this test are reported in seconds as the ratio of the patient's PT in seconds to a mean PT value of a normal population in seconds. An important advance in VKA therapy management has been the development of PT performed at the POC using native whole blood, citrated whole blood, or citrated plasma. The test result is immediately available and is reported as PT in seconds and as an international normalized ratio (INR). Reporting the INR is recommended when VKAs are monitored, because it helps reduce intersystem variation in test results.

Because accuracy of the PT depends on the thromboplastin reagent used, the World Health Organization (WHO) instituted the INR.⁵ The INR is meant to harmonize results across laboratories by calibrating each commercial thromboplastin against a WHO reference thromboplastin using a standard manual tilt-tube technique. The formula used to calculate INR uses the potency of the thromboplastin to "normalize" the PT ratio: $INR = [\text{patient PT} / \text{mean normal PT}]^{ISI}$. Thromboplastin potency is measured as the international sensitivity index (ISI). Based on sensitivity studies, lower ISI values correspond to more sensitive and responsive reagents. Reagents with lower ISIs (commonly called high-sensitivity thromboplastins) provide a therapeutic INR range that yields more precise monitoring of VKAs. For general hemostasis assessment, high-sensitivity ISI thromboplastins also enable greater elevation of the PT in seconds at lower levels of hemostasis.

Instituting harmonization using the INR has considerably improved comparability of PT results obtained with different test systems. However, even in the best-controlled studies and systems, both laboratory-based and point-of-care prothrombin time/INR (POC-PT/INR) test systems exhibit variability of INR results that increases as INR levels increase in value. This variance is exacerbated when thromboplastins from different species (eg, human and rabbit) are used. In such circumstances, it is usual to test like against like. Variance may also appear to increase when a new lot of the international reference preparation (IRP) is introduced by WHO.

Manufacturers change their calibration to the new IRP at different times, and biases between the old and new IRPs can lead to an altered bias between INR results from multiple devices. When values are compared between instruments recalibrated with



Abbreviations: ATE, allowable total error; INR, international normalized ratio.

Figure 1. Example Error Grid Demonstrating Appropriate Clinical INR Comparison Limits

In single-site comparison studies, laboratories may observe tighter overall agreement based on comparison with a single laboratory method that has been calibrated to the reference method. For example, in a clinical setting with proper system validation and installation, the agreement limits can be reduced by 5% across all ranges.

Assessing accuracy of a POC-PT/INR system should include the traditional measurements of correlation (slope, intercept, and coefficient of determination), as well as define the system bias at the critical INR decision limits (2.0, 3.0, 3.5, 4.0, and 4.5). Using the characteristics of slope and intercept, TAE (bias) is quantifiable for each PT/INR system. Calculated bias using the correlation slope and offset at the critical decision limits should fall within the stated INR agreements listed in Subchapter 4.3.2. Bias plots are visually analyzed for potential patterns of bias between each POCT device INR value and the laboratory reference INR value. The mean bias is defined as the mean difference between INR values from each POCT device and the reference laboratory. The mean percent absolute relative error of the POCT device is calculated as $|INR_{POCT} - INR_{Lab}| / INR_{Lab} \cdot 100\%$. The mean percent absolute relative error is useful, because it shows the magnitude of the difference.

Chapter 7: Quality System Essentials Considerations for Point-of-Care Coagulation Testing

This chapter includes:

- Descriptions of the quality system essentials (QSEs) as they apply to POC-CT

The QSEs apply to POCT devices in the same way they apply to laboratory-based test systems. A comprehensive QA program is essential for effective implementation of POCT. Guidance on manufacturer recommendations for QC and for health care facilities on establishing a QA program are available (see CLSI documents EP18,¹⁰⁴ EP23[™],¹⁰⁵ POCT04,² and POCT09⁴). QSEs that pertain to POC-CT include:

- Equipment Management
- Nonconforming Event Management
- Assessments

7.1 Equipment Management

General guidance on selection and evaluation of POCT devices is provided in CLSI document POCT09.⁴ Guidance on selection, evaluation, maintenance, and decommissioning of POCT devices and equipment is provided in CLSI document QMS13.¹⁰⁶ However, POCT devices differ from standard laboratory equipment in a number of ways. POCT devices are generally portable and may be directly exposed to patient blood specimens that may carry an infectious agent. Standard procedures for reducing exposure to biohazards must be followed. Decontamination of the device between tests is important to protect both patients and testing personnel. Manufacturer's instructions must be followed, because some decontamination processes (cleaning solutions or wiping methods) may damage the device.

POCT systems may have internal (ie, "on-board") control systems that check the operating integrity of the instrument to ensure it has not been damaged and is operating as intended. These instrument controls must be validated by the manufacturer to ensure strip/cartridge/cuvette defects or environmental conditions that can compromise patient results are detected. In addition to internal controls, QC solutions or electronic cartridges that can be used to verify the performance of the entire system are also available. Each manufacturer should clearly describe the QC features and recommended QC procedures for a device. The manufacturer is required to verify that the device's QC system meets regulatory and accreditation requirements. Laboratories can find information on evaluating the manufacturers' QC features using a risk assessment approach described in CLSI document EP23.¹⁰⁵

POCT devices with internal calibration features that use a bar-coded strip or a code chip that is specific to a strip/cartridge/cuvette lot are available. Calibration can be verified through a method comparison with a laboratory-based test. However, because of the variability of coagulation testing in general, it is recommended that calibration verification be performed using split specimens using the reference method described in the product insert as a comparator. As previously stated, PT/INR assays have recognized reference methods, while ACT and APTT assays do

Related CLSI Reference Materials (Continued)

- GP42** **Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens. 6th ed., 2008.** This document provides a technique for the collection of diagnostic capillary blood specimens, including recommendations for collection sites and specimen handling and identification. Specifications for disposable devices used to collect, process, and transfer diagnostic capillary blood specimens are also included.
- H21** **Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays. 5th ed., 2008.** This document provides procedures for collecting, transporting, and storing blood; processing blood specimens; storing plasma for coagulation testing; and general recommendations for performing the tests.
- H47** **One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test. 2nd ed., 2008.** This document provides guidelines for performing the PT and APTT tests in the clinical laboratory, for reporting results, and for identifying sources of error.
- H48** **Determination of Coagulation Factor Activities Using the One-Stage Clotting Assay. 2nd ed., 2016.** This guideline provides recommendations regarding the proper collection and handling of specimens, reagents, controls, calibrators, and materials needed to optimize factor assay testing. It includes recommendations for good laboratory practices related to analyzer and reagent performance, reference intervals, lot-to-lot validation, and quality control. Assay limitations and sources of errors and variability are also included.
- H54** **Procedures for Validation of INR and Local Calibration of PT/INR Systems. 1st ed., 2005.** This document describes the use of certified plasmas to enhance performance of the prothrombin time (PT)/International Normalized Ratio (INR) system test; reviews limitations of the INR systems that may occur when a manufacturer-determined ISI is used without local verification or calibration; and provides a rationale for performing local ISI verification with recommendations as to when PT calibration may be indicated. Part I is a detailed, expanded account for manufacturers and Part II is an abbreviated version useful for the clinical laboratory.
- M29** **Protection of Laboratory Workers From Occupationally Acquired Infections. 4th ed., 2014.** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.
- POCT04** **Essential Tools for Implementation and Management of a Point-of-Care Testing Program. 3rd ed., 2016.** This guideline provides direction to users of *in vitro* diagnostic devices outside the medical laboratory on how to ensure reliable results that are comparable to those obtained from medical laboratory instruments.
- POCT07** **Quality Management: Approaches to Reducing Errors at the Point of Care. 1st ed., 2010.** This document presents the core infrastructure for a standardized error tracking system with the primary goals of reducing risk and increasing quality of point-of-care testing, while accumulating standardized data for benchmarking use.
- POCT09** **Selection Criteria for Point-of-Care Testing Devices. 1st ed., 2010.** This document provides guidance on selection of point-of-care testing devices based on the patient care setting and clinical needs. It is designed as an aid to laboratory and facility management to simplify and facilitate the selection process but also allows evaluation of devices to identify those that are optimal to the patient care setting and population served.
- QMS11** **Nonconforming Event Management. 2nd ed., 2015.** Grounded in the principles of quality management, risk management, and patient safety, this guideline provides an outline and content for developing a program to manage a laboratory's nonconforming events.

Related CLSI Reference Materials (Continued)

QMS13 **Quality Management System: Equipment. 1st ed., 2011.** This guideline provides recommendations for establishing equipment management processes from selection through decommission of equipment used in the provision of laboratory services.

QMS24 **Using Proficiency Testing and Alternative Assessment to Improve Medical Laboratory Quality. 3rd ed., 2016.** This guideline describes an approach for a complete proficiency testing (PT) process and provides assistance to laboratories in using PT as a quality improvement tool.

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