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POINT-OF-CARE HEMATOLOGY AND COAGULATION TESTING IN PRIMARY, RURAL EMERGENCY, AND DISASTER CARE SCENARIOS

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Abstract

The purpose of this article is to review current principles and criteria for obtaining Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) waiver, identify existing point-of-care (POC) coagulation and hematology technologies, and analyze regulatory challenges regarding CLIA-waiver for those and future devices. CLIA '88 documentation requires tests performed by laboratories with a Certificate of Waiver to be so simple that the likelihood of erroneous results by the user is negligible, or poses no unreasonable risk of harm to the patient if performed incorrectly as determined by the Secretary of Health and Human Services. "Simple" means that the test uses unprocessed samples, has a direct read-out of test results, does not have specifications for user training, and includes instructions for confirmatory testing when advisable. Currently the CLIA-waived hematology and coagulation POC devices only test for hemoglobin (Hb), hematocrit (Hct), and prothrombin time/international normalized ratio (PT/INR). The problem with these devices is the lack of multiplexing. POC coagulation and hematology devices face challenges for obtaining a waiver. These challenges include the lack of clinical needs assessment, miniturized assays that correct for interfering substances, and assays simple enough to be combined in a multiplex platform. Several scenarios demonstrate how POC coagulation or hematology devices can improve crisis care. Industry should perform needs assessment on clinicians and emergency responders to determine which analytes to incorporate on multiplex POC coagulation and hematology devices, and produce devices that address confounding factors.

Keywords

Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) waiver; Food and Drug Administration (FDA); Clinical needs assessment (CNA); confounding factors; accuracy

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Objectives

We review principles and criteria for obtaining Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) waiver, identify point-of-care (POC) coagulation and hematology technologies, and analyze regulatory challenges. We present scenarios where POC testing could prove useful and improve the quality of care. We close with recommendations to accelerate assimilation of POC tests in emergency and disaster care, while preserving high quality test results for evidence-based medical care.

PRINCIPLES AND CRITERIA OF CLIA-WAIVER

Principles

The Food and Drug Administration (FDA) CLIA '88 Guidance Document states, “tests that may be performed by laboratories with a Certificate of Waiver, are laboratory examinations and procedures that ... have an *insignificant risk of an erroneous result*, including those that-- a) employ methodologies that are so *simple* and accurate as to render the likelihood of erroneous results by the user negligible, or b) the Secretary of Health and Human Services has determined that the method pose no unreasonable risk of harm to the patient if performed incorrectly”.¹

CLIA '88 regulates laboratories by establishing compliance standards to classify laboratories as waived, moderately complex, or highly complex depending on difficulty level of performing the test and multiple other factors. Laboratories with a Certificate of Waiver, compared to moderately or highly complex laboratories, do not need to comply with the following five standards: personnel requirements, proficiency testing, quality control, quality assurance, and patient test management.¹

Personnel with any level of education/training can be hired because routine quality control and proficiency testing is not performed.² Decreased regulation influences manufacturers to develop waived tests, but required criteria and all-inclusive data sets from field studies make successfully attaining CLIA waiver challenging and expensive for hematology and coagulation tests.

Criteria

“Simple” in waived settings requires full automation of unprocessed samples, direct read-out of test results, no specifications for user training, and instructions for confirmatory testing when advisable (Figure 1). Secondly, the device must demonstrate “insignificant risk of erroneous result” through risk analysis and flex studies that result in the creation of failure alerts and “fail-safe” mechanisms. A “fail-safe” mechanism, for example, will prohibit reporting of a result falling outside the reportable range or resulting when there is a technological malfunction.¹

By using a comparative method, the accuracy and quantitative performance of a device may be shown by plotting allowable total error (ATE) and limits of erroneous results (LER).¹ The FDA Guidance document states that “typically at least 95% of the sample results should fall within the established ATE zone... with a lower 1-sided 95% confidence bound will not exceed 92%...”¹ “Insignificant risk of erroneous result” is demonstrated by this when weighed against a comparative method.³ Even though >95% of the data points fall within this zone, the width and location of the error margin at clinically relevant values must be taken into account. Narrow ATE must fall within clinically important ranges and be supported with statistically significant sample sizes. Data falling within the zones of LER should be avoided because they could pose harm to patients if used in the clinical decision-making process.

Additionally, patient data from large multi-center clinical studies (at least three separate testing sites with a total of nine operators) should be used to define clinical performance characteristics, and specimens should be taken from the intended patient population within the specified CLIA-waived settings. The Clinical and Laboratory Standards Institute guidance document recommends manufacturers use a minimum sample size (n) of 360 specimens from the intended patient population with at least 120 samples in the low, medium, and high ranges in all clinical studies.¹

POC CLIA-WAIVED TECHNOLOGIES FOR COAGULATION AND HEMATOLOGY

Coagulation

The goal of POC testing, defined as testing at or near the site of patient care, is to improve medical and economic outcomes by promoting rapid response and faster therapeutic turnaround time (TTAT).² Faster TTAT, the time from test ordering to patient treatment, allows time-efficient management of patients in several areas within and outside the hospital. For example, the rapid measurement of a patient's prothrombin-internationalized ratio (PT-INR) in an outpatient coagulation clinic allows the clinician to make on-site therapeutic adjustments easily and quickly.

POC testing also fosters the opportunity for the patient and clinician to interact at the time of testing, taking advantage of the “teachable moment”, an opportunity to provide immediate feedback to the patient that may impact his/her risk behaviors.⁴ Table 1 lists several handheld POC devices for coagulation testing. The ProTime Microcoagulation System (International Technidyne Corporation, Edison, New Jersey)⁵ and the CoaguChek XS® System (Roche Diagnostics, Indianapolis, Indiana)⁶ analyzers are CLIA-waived for testing PT-INR using capillary fingerstick or venous samples.

These convenient, “simple”, handheld CLIA-waived devices enable patients to self-test and self-monitor their PT-INR levels, thereby improve anticoagulation control and reduce adverse events.⁷ The American College of Chest Physicians (ACCP) Guidelines recommend patient self-testing and self-monitoring be used as an effective alternative treatment model for patients undergoing anticoagulation treatment who are suitably selected and trained.⁷

Hematology

Currently, all CLIA-waived POC hematology devices test only for Hb and Hct, leaving an open market for manufacturers to produce multiplex CLIA-waived instruments. Table 2 lists several POC CLIA-waived hematology devices that utilize a variety of methods such as spectrophotometry, optical absorption photometry, and measured conductivity to determine Hb and Hct levels.

The HemoCue Hemoglobin (Hb) 301, 201+ and 201 DM Systems (HemoCue AB, Ängelholm, Sweden) are CLIA-waived for testing hemoglobin.⁸ A study by Ojengbede et al.⁹ demonstrated how the HemoCue Hb 201+ improves anemia prevention and management in Africa. Investigators found hemoglobin results from the HemoCue correlated strongly with the gold standard hemoglobincyanide method (Pearson's correlation coefficient = 0.892; $p < 0.001$). The study concluded that the HemoCue was a viable alternative from the gold standard in the prevention and management of anemia in resource poor settings.⁹

TECHNOLOGY USE IN SCENARIOS

Scenario 1: Need for accurate POC INR results to prevent thrombosis

A 45 year-old man with history of a tricuspid valve replacement on warfarin, digitalis, and a beta-blocker, presented with complaints of sudden onset of dyspnea lasting for one month. The patient had been self-monitoring his INR the past 6 months using the CoaguChek S® (Roche Diagnostics, Indianapolis, Indiana) and has obtained 12 INR test results in the range 2.6-3.9. His therapeutic range was 3.0-4.0. Upon examination, prosthetic valve sounds and a soft diastolic murmur were heard. Transthoracic echocardiography detected a dilated right ventricle with impaired function. Cine-fluoroscopy confirmed tricuspid valve dysfunction with one valve door immobile. The patient was diagnosed with obstructive thrombosis of the tricuspid prosthetic valve suspected from insufficient anticoagulation therapy as an outpatient. Laboratory INR results (2.9) were compared to POC INR (4.3) results and double-checked (Lab: 3.1; POC: 5.3) demonstrating inaccuracy of the POC device. Fibrinolytic therapy in the hospital proved effective as determined by louder valve sounds, slower velocity across the tricuspid valve, and mobile valve doors. After discharge, CoaguChek S® was replaced with CoaguChek XS® to improve high range accuracy INR > 3 to keep patient within the therapeutic range. Lesson learned: POC INR devices need to be frequently checked for accuracy to ensure proper anticoagulation management.¹⁰

Scenario 2: POC guides intravenous thrombolysis treatment

Rost et al.¹¹ performed retrospective review of data obtained from the “Get With the Guidelines Stroke” database, January 2003 to April 2008. Patients were evaluated for thrombolytic therapy eligibility using a defined stratification scheme. Patients who presented to the emergency department with onset of stroke symptoms within 3 hours (N = 470) were selected. Only 0.4% (2/470) patients had underlying coagulation abnormalities that prevented thrombolysis treatment. Rost et al.¹¹ determined that benefits from prompt administration of intravenous tissue plasminogen activator outweighed the risk of potential complications. Lippi et al.¹² point out that availability of POC devices eliminates the unnecessary risk of treating prior to receiving lab results as turnaround time for those devices is <10 minutes falling within the safe treatment window for stroke patients. According to Rizos et al.,¹³ in acute stroke, POC INR testing accelerates initiation of thrombolytic treatment (faster by 28 ± 12 minutes), with results agreeing closely with laboratory results ($r = 0.98$; $P < 0.01$). Lesson learned: POC coagulation technologies may improve outcomes of stroke patients by decreasing the rare but significant risk of harm due to unsuspected bleeding tendencies (~1% of patient cases) caused by initiating treatment prior to receiving results on coagulation abnormalities.¹¹⁻¹³

Scenario 3: Point-of-care D-dimer tests aid diagnose venous thromboembolism

The Clinical Laboratory Standards Institute (CLSI) states, “At present, none of the POC methods have been cleared by the FDA for exclusion of venous thromboembolism (VTE).” In combination, CLSI says, “When applied correctly, specifically in conjunction with the pretest probability model as part of a clinical algorithm, the use of the D-dimer assay can improve the efficiency of the evaluation of the patient suspected of having clinically relevant VTE.”¹⁴ Multiple cases of VTE were seen in the 2004 Japan Earthquake as a result of cramped conditions when victims were forced to sleep in their cars due to lack of space and privacy in mass victim shelters.¹⁵ Lesson learned: POC D-dimer can aid in clinical evaluation of patients with suspected VTE in crisis settings.

Scenario 4: POC INR monitoring improves therapeutic management and compliance in rural Australia

Three patients were enrolled in an anticoagulation monitoring study at local pharmacies in rural Australia. Patients were tested using CoaguChek S® INR device, anticoagulation therapy was adjusted as needed per INR result. Patient AB had an INR therapeutic target range of 2.5-3.5, the POC result was 5.2, as a result the patient's Warfarin dose was decreased by 1.0 mg. Patient LD had a therapeutic INR range of 2.0-3.0, had POC results of 1.2-1.4, so the patient was prescribed a dose increase of 2.0 mg. Patient LD had improved compliance which appeared to have resulted from the pharmacist using a less invasive and more convenient monitoring device. Lesson learned: Therapeutic management was enhanced by access to POC monitoring at local pharmacies in rural settings, which demonstrates the feasibility of integrating POC INR devices in remote and rural health care systems.¹⁶

Scenario 5: Value of a mobile, POC anticoagulation therapy management program

Gill et al.¹⁷ demonstrated the impact of a mobile multisite office-based anticoagulation therapy management (ATM) program in seven cardiology clinics in three counties in Delaware. A trained nurse rotated between seven rural, urban, and suburban community clinics. Two hundred patients visited the ATM clinics and received POC INR testing, medication adjustment based on physician-approved algorithm, and education on dietary habits that affect INR levels. They found that before the ATM, 40.7% (81.4/200) patients were within the target INR range 2.0-3.0, and after the ATM was implemented 58.5% (117/200) patients were within range ($P<0.001$). Lesson learned: Use of a mobile multisite outpatient POC ATM program led to improved anticoagulation clinic management and increased number of patients within the therapeutic target range.¹⁷

CLIA-WAIVED TESTS FOR EMERGENCY AND DISASTER CARE SETTINGS

Within the context of emergency and disaster care, CLIA-waived POC hematology devices may be useful where faster TTAT is needed. For example, during a nuclear mass casualty, serial complete blood counts (CBCs) with WBC differential, such as absolute lymphocyte count can be used to assess the severity of radiation exposure in victims. Hematologists and oncologists participating in the Radiation Injury Treatment Network (RITN) may find POC hematology devices helpful by providing faster TTAT for exposed patients requiring urgent treatment.¹⁸⁻²⁰ For critical care, the rapid diagnosis of hyperleukocytosis in an oncological emergency along with quick WBC monitoring with a POC device can prompt life-saving management and treatment such as induction chemotherapy and leukapheresis.³

CHALLENGES OF CLIA-WAIVER

Clinical Needs Assessment

One challenge in influencing industry to develop CLIA-waived POC hematology devices is identifying a clinical need. For example, the HemoCue Hb 201+ system provides blood banks with immediate pre-transfusion hemoglobin levels of donor blood as part of the screening process.

However, CLIA-waived POC hematology devices are not equipped for home use though this could be a future aim for industry, the problem is that the end-user must not only be able to administer the test but most importantly, have the ability to interpret the results correctly or relay them to their medical provider. This is a significant problem in the realm of hematology since interpretation usually requires clinical correlation with results of several hematological parameters. Therefore, with a specified intended use and clinical need for a

test to be CLIA-waived, clinical studies can be tailored to demonstrate the test as “simple” with an “insignificant risk of erroneous result”.

Clinical needs assessment plays a significant role in defining end-user needs. Kost, et al.²¹⁻²³ used surveys targeting disaster medicine experts to determine future point-of-care designs, instrument characteristics, and test clusters for POC tests use in emergency and disaster care with a focus on infectious disease testing. Future surveys need to be extended to point-of-service hematology and coagulation tests.

Focus groups consisting of physicians, laboratorians, and academicians can provide input on test parameters that will deliver the most clinical impact, such as target diseases, conditions and patient populations in waived settings, and expectations for operator competence, quality control, and diagnostic interpretations. Limitations for use in waived setting must be established to mitigate the risk of erroneous results, and regulations regarding quality assurance must be reassessed.¹

Test Menu

For hematology testing, a multiplex device should be available for clinicians to make proper clinical assessments. The instrument should distinguish target analytes from interfering substances in blood that cause false-positive or negative results in qualitative systems or falsely elevated or depressed results in quantitative systems, all of which can impact clinical care.²

Reticulocytes (immature red blood cells) and more than 2% of circulating nucleated red blood cells (nRBCs) represent two interfering substances with the WBC count. One of the current CLIA-waived POC hematology instruments does not distinguish between nRBCs and WBCs due to its image analysis program not separating nRBCs from total WBC and having too short of a reaction time to overcome the stronger resistance to lysis in reticulocytes.²⁴ Osei-Bimpong et al,²⁴ found that reticulocyte and nRBC levels are elevated in hemoglobinopathies, especially sickle cell disease and thalassaemia major. Reporting nRBCs as a quantitative result will not only preclude it as an interfering substance but may prove to be clinically useful. For example, Stachon et al.²⁵ discovered that nRBCs in a patient sample could be an indication of poor prognosis due to endotoxemia or hypoxia in critically ill patients. This marker can be used to help clinicians decide whether or not to transfer the patient to other units within the hospital.²⁵ In addition, nRBCs may indicate hemolytic disease in newborns or intrauterine hypoxemia resulting in further clinical investigation.²⁶⁻²⁸

A POC hematology device intended for an outpatient oncology clinic setting must include a comprehensive set of analytes for the intended patient population in the specified waived setting. For example, the absolute neutrophil count (ANC) consists of absolute number of segmented neutrophils and bands, and plays an important role in deciding when to hold or reduce chemotherapy, increase myeloid growth factor treatment ($ANC < 1.8 \times 10^9/L$), or increase antibiotics ($ANC < 0.5 \times 10^9/L$).^{29,30} Table 3 shows critical therapeutic decision levels for clinically important parameters such as ANC and nRBCs.

EMERGING TECHNOLOGIES

Due to technological advancements, future multiplex POC hematology devices may have the capacity to fulfill FDA criteria for CLIA-waiver. Current near-patient (benchtop) POC hematology analyzers such as the Coulter AC•T Diff™ (Beckman Coulter, Palo Alto, California)³¹ can test for up to 18-parameters including a full complete blood count (CBC) with 5-part differential (absolute and proportional counts), hemoglobin, hematocrit, and red

blood cell (RBC) differential. Analyzers capable of reporting both absolute and proportional counts for different white blood cell (WBC) types can help improve clinical assessment, as recommended by the College of American Pathologists (CAP) Hematology and Clinical Microscopy Resource Committee and the Clinical Laboratory Standards Institute (CLSI).²⁹ A CLIA-waived POC device with these capabilities that is portable or handheld could further improve clinical assessment in remote clinical, emergency, and disaster settings (Figure 2). Use of wireless communication could be an addition to future POC hematology and coagulation devices to allow them to obtain a CLIA-waiver for home-use. The wireless communication or “smart medicine” concept eliminates the need for user knowledge of the test by relaying results to the patients primary care provider.

CONCLUSIONS

POC devices provide several technological solutions that help meet CLIA-waiver criteria. Minimal preanalytical steps reduce user variability, error, and simplifies the test. Internal controls and flagging of abnormal results help to mitigate erroneous results. CLIA-waived tests can be performed by any person, creating a dependency on them to know how what to do with the results. Whether or not the user will be able to administer the test and know what to do with the results or relay the them to the their medical provider, presents a problem that CLIA-waived hematology and coagulation tests face. Therefore, technological solutions to compensate for user knowledge or user ability to convey results should be required, this may be accomplished via wireless communication or through use of “smart medicine” where the device will inform the patient to seek treatment if the results are interpreted as an alert or critical value.

RECOMMENDATIONS

Multiplex POC hematology testing provides added value to enhancing the delivery of clinical care in emergency and disaster settings, primary and urgent care settings, and could prove useful at home and offers the capability of monitoring/diagnostic testing in rural and low resource environments. Industry should continue to work with industry to design the POC test menu that provides the most clinical value. Industry should consider developing automated POC hematology & coagulation devices that qualify for a CLIA-waiver, so they can be readily placed in physicians offices and clinics in remote settings. The devices also need to be able to interpret results for their users and be able to communicate the results to patients medical provider. These tests need to be highly accurate and be able to discriminate potential confounding factors. The ATE of POC tests need to be determined taking clinically relevant values into account to impact clinical decision-making.

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Figure 1. Device Requirements to Obtain CLIA-waiver
There are seven categories that devices need to score a 1 in to obtain a CLIA-waiver (1 = lowest complexity, 3 = highest complexity). Each box describes the requirements for a device to score a 1 in the different categories.

Figure 2. Emerging Technology Logic Model

Performing a clinical needs assessment should result in a clinically relevant test menu that users would prefer to have on POC devices. It would also show that they prefer the POC devices to be small and handheld, require no sample processing, alert the user of critical values, and wirelessly communicate the results. This information would go to device developers to produce CLIA-waived technology with these capabilities that are usable in homes, hospitals, clinics, ambulances, and alternate care facilities. The devices produced will assist in new clinical needs assessments through user feedback.

Table 1

Portable and/or Handheld CLIA Waived POC Coagulation Devices

<u>Instrument/Manufacturer</u>	<u>Method</u>	<u>Test</u>
CoaguChek XS Plus System Roche Diagnostic www.roche-diagnostics.com	Electrochemical measurement of PT following activation	PT/INR
CoaguChek XS System Roche Diagnostic www.roche-diagnostics.com	Electrochemical measurement of PT following activation	PT/INR
Coagu-Sense™ PT/INR Monitoring System Coagu-Sense, Inc. www.coagusense.com	Detecting clot formation	PT/INR
INRatio®/INRatio@2 PT/INR Monitoring System Alere™ www.alere.com	Electrochemical system based on change of impedance when clot occurs	PT/INR
ProTime® Microcoagulation System International Technidyne Corp. www.itcmed.com	Photochemical system based on fibrin formation	PT/INR

Abbreviations: PT/INR, prothrombin time/ international normalized ratio

Table 2

Portable and/or Handheld CLIA Waived POC Hematology Devices

<u>Instrument/Manufacturer</u>	<u>Method</u>	<u>Test(s)</u>
HgbPro International Technidyne Corp. www.itcmed.com	Optical measurement of membrane reflectance	Hb
Hemo Control EKF Diagnostics www.efkdiagnostics.de	Photometric cyanmethemoglobin	Hb [*] , Hct ^a
HemoCue® Donor Hb Checker System HemoCue® AB www.hemocue.com	Spectrophotometry	Hb
HemoCue® Hb 201 DM System HemoCue® AB www.hemocue.com	Spectrophotometry	Hb
HemoCue® Hb 201+ System HemoCue® AB www.hemocue.com	Spectrophotometry	Hb
HemoCue® Hb 301 system HemoCue® AB www.hemocue.com	Spectrophotometry	Hb
HemoPoint® H2 Meter Alere www.alere.com	Optical absorption photometry	Hb
HemoPoint® H2 DMS Stanbio Laboratory www.stanbio.com	Optical absorption photometry	Hb [*] , Hct ^a
HemoPoint® H2 Photometer Stanbio Laboratory www.stanbio.com	Optical absorption photometry	Hb [*] , Hct ^a
i-STAT® System Abbott Point of Care Inc. www.abbottpointofcare.com	Measured Conductivity	Hb, Hct ^a
STAT-Site® MHgb Hemoglobin Photometer Stanbio Laboratory www.stanbio.com	Reflectance photometry	Hb
UltraCrit™ Separation Technology Inc. www.separationtechnology.com	Ultrasound	Hct

Abbreviations: Hb, Hemoglobin; Hct, Hematocrit

* Device is only CLIA waived for this analyte;

^a calculated value

Table 3

When to use nRBCs and ANC for Diagnosis and Monitoring

<u>Assay</u>	<u>Critical Levels</u>	<u>Associated With</u>
ANC	$>6.8 \times 10^9/L$	Infections, variety of inflammatory disorders, cytokine therapy, and some myeloid neoplasms. ⁸
	$<1.8 \times 10^9/L$	Chemotherapy, toxins, bone marrow replacement, myelodysplastic syndromes, autoimmune disorders, and congenital disorders. ⁸
	$0.5 - 1.0 \times 10^9/L$	Some propensity for infection ⁸
	$<0.5 \times 10^9/L$	Significantly increased propensity for serious infection ⁸
nRBCs	$200 \times 10^6/L$	100% mortality in patients undergoing (Pre-engraftment) and have undergone (postengraftment) stem cell transplantation ³²