H49-A
Vol. 24 No. 23
Replaces H49-P
Vol. 23 No. 23

Point-of-Care Monitoring of Anticoagulation Therapy; Approved Guideline

This document provides guidance to users and manufacturers of point-of-care coagulation devices for monitoring heparin and warfarin anticoagulant therapy, and to ensure reliable results comparable to those obtained by routine clinical laboratory testing.

A guideline for global application developed through the NCCLS consensus process.

NCCLS

NCCLS...

Global Consensus Standardization for Health Technologies

NCCLS is an international, interdisciplinary, nonprofit, standards-developing, and educational organization that promotes the development and use of voluntary consensus standards and guidelines within the healthcare community. It is recognized worldwide for the application of its unique consensus process in the development of standards and guidelines for patient testing and related healthcare issues. NCCLS is based on the principle that consensus is an effective and cost-effective way to improve patient testing and healthcare services.

In addition to developing and promoting the use of voluntary consensus standards and guidelines, NCCLS provides an open and unbiased forum to address critical issues affecting the quality of patient testing and health care.

PUBLICATIONS

An NCCLS document is published as a standard, guideline, or committee report.

Standard A document developed through the consensus process that clearly identifies specific, essential requirements for materials, methods, or practices for use in an unmodified form. A standard may, in addition, contain discretionary elements, which are clearly identified.

Guideline A document developed through the consensus process describing criteria for a general operating practice, procedure, or material for voluntary use. A guideline may be used as written or modified by the user to fit specific needs.

Report A document that has not been subjected to consensus review and is released by the Board of Directors.

CONSENSUS PROCESS

The NCCLS voluntary consensus process is a protocol establishing formal criteria for:

- the authorization of a project
- the development and open review of documents
- the revision of documents in response to comments by users
- the acceptance of a document as a consensus standard or guideline.

Most NCCLS documents are subject to two levels of consensus—"proposed" and "approved." Depending on the need for field evaluation or data collection, documents may also be made available for review at an intermediate consensus level.

Proposed An NCCLS consensus document undergoes the first stage of review by the healthcare community as a proposed standard or guideline. The document should receive a wide and thorough technical review, including an overall review of its scope, approach, and utility, and a line-by-line review of its technical and editorial content.

Approved An approved standard or guideline has achieved consensus within the healthcare community. It should be reviewed to assess the utility of the final document, to ensure attainment of consensus (i.e., that comments on earlier versions have been satisfactorily addressed), and to identify the need for additional consensus documents.

NCCLS standards and guidelines represent a consensus opinion on good practices and reflect the substantial agreement by materially affected, competent, and interested parties obtained by following NCCLS's established consensus procedures. Provisions in NCCLS standards and guidelines may be more or less stringent than applicable regulations. Consequently, conformance to this voluntary consensus document does not relieve the user of responsibility for compliance with applicable regulations.

COMMENTS

The comments of users are essential to the consensus process. Anyone may submit a comment, and all comments are addressed, according to the consensus process, by the NCCLS committee that wrote the document. All comments, including those that result in a change to the document when published at the next consensus level and those that do not result in a change, are responded to by the committee in an appendix to the document. Readers are strongly encouraged to comment in any form and at any time on any NCCLS document. Address comments to the NCCLS Executive Offices, 940 West Valley Road, Suite 1400, Wayne, PA 19087, USA.

VOLUNTEER PARTICIPATION

Healthcare professionals in all specialties are urged to volunteer for participation in NCCLS projects. Please contact the NCCLS Executive Offices for additional information on committee participation.

H49-A
ISBN 1-56238-540-2
Volume 24 Number 23
ISSN 0273-3099

Point-of-Care Monitoring of Anticoagulation Therapy; Approved Guideline

J. Heinrich Joist, M.D., Ph.D.
Jack E. Ansell, M.D.
George G. Despotis, M.D.
Frank LaDuca, Ph.D.
Richard A. Marlar, Ph.D.
Ginette Y. Michaud, M.D.
David L. Phillips
Paula J. Santrach, M.D.

Abstract

Point-of-care coagulation testing (POC-CT), also known as “bedside testing” or “near-patient testing,” is intended to provide test results more rapidly than can be achieved in hospital or reference laboratory settings. This is important in intensive care units, emergency rooms, operating rooms, and outpatient clinics, where it may help to expedite treatment decisions. POCT allows coagulation testing in the home environment, including patient self-testing (PST), thus providing increased access and convenience for the patient and/or caregiver and improving quality of care.

The guideline provides users of POC-CT systems with information and suggestions for good clinical testing practice and for producing reliable test results regardless of where or by whom the test is performed. This document deals with POC-CT performed for monitoring heparin and warfarin therapy.

NCCLS. *Point-of-Care Monitoring of Anticoagulation Therapy; Approved Guideline*. NCCLS document H49-A (ISBN 1-56238-540-2). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2004.

NCCLS

Suggested Citation

(NCCLS. *Point-of-Care Monitoring of Anticoagulation Therapy; Approved Guideline.* NCCLS document H49-A [ISBN 1-56238-540-2]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2004.)

Proposed Guideline
September 2003

Approved Guideline
July 2004

ISBN 1-56238-540-2
ISSN 0273-3099

Committee Membership

Area Committee on Hematology

Bruce H. Davis, M.D.
Chairholder
Maine Medical Center Research Institute
Scarborough, Maine

Samuel J. Machin, MB, Ch.B, FRCPath, FRCP
Vice-Chairholder
The University College London Hospitals
London, United Kingdom

Dorothy M. Adcock, M.D.
Esoterix Coagulation
Aurora, Colorado

Frank M. LaDuca, Ph.D.
International Technidyne Corporation
Edison, New Jersey

Ginette Y. Michaud, M.D.
Center for Devices and Radiologic Health
Food and Drug Administration
Rockville, Maryland

Albert Rabinovitch, M.D., Ph.D.
Hematology Business Unit
Abbott Diagnostics Division
Santa Clara, California

Maryalice Stetler-Stevenson, M.D., Ph.D.
National Institutes of Health
Bethesda, Maryland

Advisors

Charles F. Arkin, M.D.
Lahey Clinic
Burlington, Massachusetts

J. David Bessman, M.D.
University of Texas Medical Branch
Galveston, Texas

Sheila Clover, CPT(ASCP)(NCA)
Phlebotomy West
Brentwood, California

Dennis J. Ernst, M.T.(ASCP)
Center for Phlebotomy Education
Ramsey, Indiana

John A. Koepke, M.D.
Durham, North Carolina

Francis Lacombe, M.D., Ph.D.
Hôpital Haut-Lévêque
Pessac, France

Richard A. Marlar, Ph.D.
Oklahoma City VA Medical Center
Oklahoma City, Oklahoma

Diane I. Szamosi, M.A., M.T.(ASCP)SH
Greiner Bio-One,
VACUETTE North America, Inc.
Monroe, North Carolina

Luc Van Hove, M.D., Ph.D.
Abbott Laboratories
Abbott Park, Illinois

Subcommittee on Point-of-Care Coagulation Testing

Jack E. Ansell, M.D.
Chairholder
Boston University Medical Center
Boston, Massachusetts

George G. Despotis, M.D.
Washington University School of Medicine
St. Louis, Missouri

Frank M. LaDuca, Ph.D.
International Technidyne Corporation
Edison, New Jersey

Richard A. Marlar, Ph.D.
Denver VA Medical Center
Denver, Colorado

Ginette Y. Michaud, M.D.
FDA Center for Devices/Rad. Health
Rockville, Maryland

David L. Phillips
i-Stat Corp.
East Windsor, New Jersey

Paula J. Santrach, M.D.
Mayo Clinic
Rochester, Minnesota

Advisors

Sue S. Beglinger, M.S., M.T.(ASCP)
University of Wisconsin
Madison, Wisconsin

J. David Bessman, M.D.
University of Texas Medical Branch
Galveston, Texas

Mary F. Cavin
John L. McClellan Memorial VA Hospital
Irvine, California

W. Gregory Cooper
Bio-Rad Laboratories, ECS Division
Indianapolis, Indiana

Catherine Cox, M.D.
Methodist Hospital of Indiana
Indianapolis, Indiana

Amando D'Angelo
H.S. Raffaele
Milan, Italy

Paul A. Foster, M.D.
Abbott Laboratories
Abbott Park, Illinois

Kenneth D. Levy
Roche Diagnostics Corporation
Indianapolis, Indiana

Marilyn Lightfoote
FDA Center for Devices/Rad. Health
Rockville, Maryland

Janice Marks
Health Park Medical Center
Fort Myers, Florida

Valerie L. Ng, Ph.D., M.D.
San Francisco General Hospital
San Francisco, California

John D. Olson, M.D.
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Staff

David E. Sterry, M.T.(ASCP)
Staff Liaison
NCCLS
Wayne, Pennsylvania

Donna M. Wilhelm
Editor
NCCLS
Wayne, Pennsylvania

Melissa A. Lewis
Assistant Editor
NCCLS
Wayne, Pennsylvania

Acknowledgement

NCCLS gratefully acknowledges the late Dr. J. Heinrich Joist, St. Louis University Health Sciences Center, who served as the Chairholder from the development through the completion of the proposed-level guideline.

Contents

Abstract i

Committee Membership iii

Foreword vii

1 Scope 1

2 Introduction 1

3 Standard Precautions 1

4 Definitions 1

5 Point-of-Care Coagulation Testing (POC-CT)—General Considerations 6

6 Quality Management: General Considerations for Point-of-Care Coagulation Testing 6

- 6.1 Operators, Materials, and Performance of POC-CT 6
- 6.2 Training 7
- 6.3 Quality Control and Proficiency Testing 8
- 6.4 Result Recording and Reporting 9

7 Monitoring Heparin Therapy 10

- 7.1 Introduction 10
- 7.2 Blood Specimen Collection and Handling 11
- 7.3 POC-CT Systems Used for Monitoring Heparin Therapy 11
- 7.4 Specific Applications 14

8 Monitoring Warfarin Therapy 15

- 8.1 Introduction 15
- 8.2 Blood Specimen Collection and Handling 15
- 8.3 Test Systems Used for Monitoring Warfarin Therapy 16
- 8.4 Specific Applications 18
- 8.5 Result Recording and Reporting 19

References 20

Summary of Delegate Comments and Subcommittee Responses 22

The Quality System Approach 26

Related NCCLS Publications 27

Foreword

Medical conditions, physical location of the patient, and treatment regimens often require test results to be obtained quickly, so appropriate medical care can be administered expeditiously. Laboratory medicine professionals are challenged by the increasing demands for providing faster turnaround of test results, without compromising accuracy. The need to provide test results at greater convenience to, and increased efficiency for, the patient/caregiver without compromising cost-effectiveness is also recognized.

With the introduction of portable devices capable of producing results within seconds or minutes, point-of-care testing (POC—also referred to as "near-patient testing" or "bedside testing"), has been evolving as one way to meet these demands. Because of the potentially serious consequences of inaccurate test results, it is essential that results are accurate and reliable.

One of the challenges facing the healthcare community is acceptance of the idea that clinical coagulation testing, traditionally performed by and under the supervision of trained laboratory professionals, may be performed by personnel not trained in clinical laboratory practice or by patients/caregivers in the home. However, it is the responsibility of the manufacturer to provide test systems capable of delivering accurate results when used properly. 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 within the hospital, e.g., operating room, emergency room, intensive care unit, postsurgical recovery room, hemodialysis unit, ambulatory care site, and the patient's home. The selection of patients for patient self-testing (PST) is the responsibility of the treating physician.

This document provides information to users on how to proceed in the evaluation, implementation, and monitoring of POC-CT, and deals only with the use of POC-CT in monitoring of anticoagulant therapy. It does not address issues related to the use of POC-CT in the evaluation of patients with suspected bleeding disorders. The guideline was written under the assumption that most users may not be laboratory professionals and provides important definitions, procedures, and recommendations. The format is designed to be easy to follow for the lay user.

This document relates closely to NCCLS documents EP18—*Quality Management for Unit-Use Testing* and AST2—*Point-of-Care* In Vitro *Diagnostic (IVD) Testing*. Please refer to these documents for additional information.

A Note on Terminology

NCCLS, as a global leader in standardization and harmonization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. NCCLS recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in NCCLS, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all obstacles to harmonization. In light of this, NCCLS recognizes that harmonization of terms facilitates the global application of standards and is an area of immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In order to align the terminology used in H49-A with ISO, the term "trueness" is used in this document when referring to the closeness of the agreement between the average value from a large series of measurements to a true value of a measurand. The term "accuracy," in its metrological sense, refers to the closeness of the agreement between the result of a (single) measurement and a true value of a measurand, thus comprising both random and systematic effects.

All terms and definitions will be reviewed again for consistency with international use, and revised appropriately during the next scheduled revision of this document.

The Subcommittee on Point-of-Care Coagulation Testing appreciates the opinions of manufacturers and users of POC-CT devices. We encourage all to participate in the consensus process by submitting written comments on content and format to the NCCLS Executive Offices. The subcommittee will consider all comments when it revises this guideline for the next edition.

Key Words

Calibration, point-of-care testing, quality assurance, quality control, safety

Point-of-Care Monitoring of Anticoagulation Therapy; Approved Guideline

1 Scope

This document deals only with the use of POC-CT in monitoring of anticoagulant therapy with unfractionated heparin (hereafter called "heparin") and warfarin. It does not address issues related to the use of POC-CT in the evaluation of patients with suspected hemostatic disorders or use of other anticoagulants. There are many potential sites for POC-CT, such as hospitals, physicians' offices, and patients' homes. Those performing POC-CT may include healthcare professionals and patient caregivers, as well as patients.

2 Introduction

Advances in technology and the development of microtechniques and portable test instruments have made it possible to move medical testing closer to the patient. Point-of-care coagulation testing (POC-CT), is intended to provide test results more rapidly, efficiently, and conveniently than can be achieved in the clinical laboratory. This is particularly important in intensive care units, emergency rooms, operating rooms, and outpatient clinics where it may help expedite treatment decisions. POC-CT may also provide greater access to testing for the patient and/or caregiver, whether in the clinic or home setting. POC-CT may also reduce errors due to incorrect or delayed test result transmission to the patient/caregiver and thus improve overall quality of care. The guideline provides information and suggestions for good medical testing practice to produce accurate test results regardless of where, and by whom, testing is performed.

3 Standard Precautions

Because it is often impossible to know what might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all infectious agents and thus are more comprehensive than universal precautions which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the U.S. Centers for Disease Control and Prevention (*Guideline for Isolation Precautions in Hospitals*. Infection Control and Hospital Epidemiology. CDC. 1996;17(1):53-80 and *MMWR* 1988;37:377-388). For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to the most current edition of NCCLS document M29—*Protection of Laboratory Workers from Occupationally Acquired Infections*.

4 Definitions

Accuracy (of measurement) – Closeness of the agreement between the result of a measurement and a true value of the measurand (VIM93)[1]; **NOTE:** See **Measurand**.

Activated clotting time, ACT – A global coagulation test which is particularly sensitive to abnormalities in the intrinsic blood coagulation pathway and the anticoagulant activity of heparin; **NOTE:** The ACT is a measurement of the time in seconds required for a clot to form in a native (i.e., nonanticoagulated) blood specimen which has been exposed to a contact activator of the intrinsic phase blood coagulation pathway.

Activated partial thromboplastin time, APTT – A global coagulation test used for the evaluation of the intrinsic and common coagulation pathway and for monitoring therapy with unfractionated heparin and certain other anticoagulants; **NOTE:** The APTT is the time in seconds required for a fibrin clot to form in a plasma sample after an optimal amount of calcium chloride, a partial thromboplastin reagent (phospholipid), and a contact factor activating agent have been added to the sample.

Anticoagulant – An agent, natural or pharmacological, that inhibits clotting of blood or plasma.

Antithrombin, AT (formerly Antithrombin III) – A plasma protein which, when activated by heparin or heparin-like molecules containing a specific pentasaccharide sequence such as glucosaminoglycans on endothelial cells, is a potent, irreversible inhibitor of activated, procoagulant serine proteases such as thrombin and Factor Xa.

APTT (POC) – The APTT performed using a point-of-care (POC) test system.

Bias – The difference between the expectation of the test results and an accepted reference value (ISO 3534-1).[2]

Blood specimen – The discrete portion of blood taken for examination, study, or analysis of one or more quantities or characteristics to determine the character of the whole.

Arterial – Blood obtained by arterial puncture or from an individual arterial line, catheter, or extracorporeal circuit.

Capillary – Blood obtained by skin puncture.

Venous – Blood obtained by venipuncture or from an indwelling line or catheter.

Calibration – Set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards (VIM93)[1]; **NOTE:** According to the U.S. Code of Federal Regulations, calibration is the process of testing and adjustment of an instrument, kit, or test system, to provide a known relationship between the measurement response and the value of the substance being measured by the test procedure (US CFR 493 February 28, 1992).[3]

Cardiopulmonary bypass, CPB – A procedure used to sustain organ perfusion with oxygenated blood during cardiac surgery.

Coagulation test system – A device used to measure the rate of clotting of blood or plasma.

Common blood coagulation pathway – The activation of Factor X by Tissue Factor/VIIa complex and/or Factor IXa, followed by activation of Factor II and conversion of fibrinogen to fibrin.

Competency assessment – Evaluation of a person's ability to perform a test including all aspects of testing, from specimen collection to result reporting.

Contact activator – A particulate (e.g., kaolin, celite, silica) or soluble (e.g., ellagic acid) substance which activates the "contact phase of coagulation," involving Hageman Factor (Factor XII), Prekallikrein, and HMW Kininogen, thereby initiating the intrinsic phase blood coagulation pathway (i.e., activation of Factors XI and IX).

Control/control material – A device, solution, or lyophilized preparation intended for use in the quality control process to monitor the reliability of a test system and to maintain its performance within established limits; **NOTE:** The expected reaction or concentration of analytes of interest are known within limits ascertained during preparation and confirmed in use.

Correlation – The degree to which two variables are proportionally related to each other; **NOTE:** High method correlation does not imply high numeric agreement of analytic results, but only the predictability of one method's results by the other method.

Extrinsic blood coagulation pathway – The activation of Factor X by Tissue Factor/VIIa complex.

Hemodialysis – A procedure used to remove toxic substances from blood in patients with severe renal failure.

Heparin (unfractionated) – A mixture of complex glycosaminoglycans (mucopolysaccharides) of widely varying molecular weight (5000 – 50 000 d) derived from animal tissues, used for prevention and treatment of venous and arterial thrombosis.

Imprecision – Dispersion of independent results of measurements obtained under specified conditions; **NOTE:** It is expressed numerically as standard deviation or coefficient of variation.

International normalized ratio, INR – Expression of the patient's prothrombin time (PT) test result expressed as a ratio to a normal population control which has been standardized (or normalized) for the potency to the thromboplastin used in the assay; **NOTES:** a) The INR is determined by using the equation: $INR = R^{ISI}$, where R is the PT ratio obtained with the working thromboplastin; b) The ISI should be determined by standard protocols according to WHO guidelines and provided by the manufacturer to the user for a particular reagent/instrument combination or POC-CT system.

International sensitivity index, ISI – A mathematical indicator of the responsiveness of a PT testing system to deficiencies of the vitamin K coagulation factors; **NOTES:** a) It is the comparative slope used to calculate the INR; b) A low ISI indicates a highly responsive PT system and a high ISI indicates a poorly responsive system; c) It is determined by standard protocols according to WHO guidelines and provided by the manufacturer to the user for a particular reagent/instrument combination.

Intrinsic phase blood coagulation pathway – The sequential activation of Factors XII, XI, and IX in the presence of Prekallikrein and co-factors HMW-Kininogen and Factor VIII triggered by contact factor.

Measurand – Particular quantity subject to measurement; (VIM93-2.6). **NOTE 1:** [VIM93-2.6] For example, vapour pressure of a given sample of water at 20 °C; **NOTE 2:** [VIM93-2.6] The specification of a measurand may require statements about quantities such as time, temperature and pressure; **NOTE 3:** [NRSCL8] This term and definition encompass all quantities, while the commonly used term "analyte" refers to a tangible entity subject to measurement. For example, "substance" concentration is a quantity that may be related to a particular analyte.

Native whole blood – Blood withdrawn into a syringe or tube to which no additives, such as anticoagulants, are added.

Patient self-testing, PST – The testing by a patient or caregiver on blood or body fluid obtained from the patient.

Percutaneous coronary intervention, PCI – Any one of a number of intervention procedures in which a catheter is inserted into a coronary artery for the purpose of removing obstruction by an atherosclerotic

plaque; these include percutaneous transluminal coronary angioplasty (PTCA), atherectomy, and coronary stent placement.

Plasma – *In vivo*, the liquid portion of whole blood that does not contains cells; *in vitro*, the liquid portion of anticoagulated whole blood that does not contain cells.

POC-APTT – See **APTT (POC)**.

POC-PT – See **PT (POC)**.

Point-of-care (POC) testing//bedside, near-patient testing – Testing performed in an alternate site, outside a central laboratory environment, generally nearer to, or at the site of, the patient.

Precision – The closeness of agreement between independent measurement results obtained under stipulated conditions (ISO 3534-1)[2]; **NOTE:** Precision is not typically represented as a numerical value but is expressed quantitatively in terms of imprecision—the standard deviation (SD) or the coefficient of variation (CV) of the results in a set of replicate measurements (ISO 3534-1).[2]

Proficiency testing (quality assessment scheme) – Determination of laboratory testing performance by means of interlaboratory comparisons; **NOTES:** a) Commonly, a program periodically sends multiple specimens to members of a group of laboratories for analysis and/or identification; the program then compares each laboratory's results with those of other laboratories in the group and/or with an assigned value, and reports the results to the participating laboratory and others; b) The results are summarized, analyzed, and, with some tests, graded by the program and provided to the participating site which can compare its results with those of other sites that use a similar method; c) Other forms of PT/EQA include: data transformation exercises, single-item testing (where one item is sent to a number of laboratories sequentially and returned to the program at intervals), and one-off exercises (where laboratories are provided with a test item on a single occasion).

Prothrombin time, PT – The time in seconds required for a fibrin clot to form after tissue thromboplastin and an optimal amount of calcium chloride have been added to a plasma sample.

Prothrombin time test – A coagulation test sensitive to abnormalities of the extrinsic and common coagulation pathway;

PT (POC) – The PT performed using a point-of-care test system.

PT ratio – The PT of a test plasma divided by the geometric mean of the normal PT reference range; **NOTE:** The PT ratio is used to calculate the international normalized ratio (INR).

Quality assurance, QA – All the planned and systematic activities implemented within the quality system and demonstrated as needed, to provide adequate confidence that an entity will fulfill requirements for quality (ISO8402:94-3.5); **NOTE:** QA includes monitoring, evaluating, taking corrective actions, if necessary and monitoring the corrective actions for preanalytical, analytical, and post-analytical activities; these activities include, but are not limited to, recordkeeping, calibration and maintenance of equipment, quality control, proficiency testing, and training.

Quality control, QC – In healthcare testing, a set of procedures designed to monitor the test method, and the results to assure optimal test system performance; **NOTE:** QC includes testing of normal and abnormal control materials, recording the results, identifying sources of error, and evaluating and documenting any corrective action taken.

Reagent – A substance that produces a chemical reaction in a sample that allows an analyte to be detected and/or measured.

Sample – In this document, a sample taken from the patient specimen and used to obtain information by means of a specific laboratory test.

Sensitivity (analytical) – The change in response of a measuring system or instrument divided by the corresponding change in the stimulus (modified from VIM93)[1]; **NOTES:** a) The sensitivity may depend on the value of the stimulus (VIM93)[1]; b) The sensitivity depends on the imprecision of the measurements of the sample.

Skin puncture – Breakage of skin with a needle or lancet to produce blood for collection and testing.

Stability – The capacity of a product to retain its composition, characteristics, and properties during specified conditions.

Testing site – The physical location where testing is performed.

Tilt tube – A means of determining the clotting endpoint of an *in vitro* coagulation assay; **NOTES:** a) The determination is usually performed by the visual observation of the back-and-forth movement of plasma in a test tube to which reagents have been added to stimulate coagulation; b) The endpoint of the tilt tube assay is the appearance of a fibrin clot.

Time-in-therapeutic range, TTR – A quality measure of therapeutic effectiveness for patients on oral anticoagulants; **NOTE:** Depending on the methodology used to measure it, it represents either estimated time (days) spent in a patient-specific therapeutic range or the percent of INRs in therapeutic range.

Trueness – The closeness of agreement between the average value obtained from a large series of test results and an accepted reference value; (ISO 3534-1)[2]; **NOTES:** a) Trueness is usually expressed numerically by the statistical measure bias that is inversely related to trueness; b) See also **Accuracy** and **Bias.**

Validation – Confirmation through the provision of objective evidence, that requirements for a specific intended use or application have been fulfilled (ISO 9000)[4]; **NOTES:** a) WHO defines validation as the action {or process} of proving that a procedure, process, system, equipment, or method used works as expected and achieves the intended result (WHO-BS/95.1793)[5]; b) The components of validation are quality control, proficiency testing, validation of employee competency, instrument calibration, and correlation with clinical findings.

Venipuncture – The puncture of a vein for surgical or therapeutic, purposes, or for collecting blood specimens for analysis (RHUD1.7CD) (Cf. H3).

Venous thromboembolism, VTE – A term commonly used for the closely linked conditions of deep vein thrombosis and pulmonary embolism.

Verification – Confirmation through the provision of objective evidence that specified requirements have been fulfilled (ISO 9000)[4]; **NOTE:** A one-time process completed to determine or confirm test performance characteristics before the test system is used for patient testing.

Whole blood – Blood that contains all of its cellular and plasma components; **NOTES:** a) It may be collected in an anticoagulant solution, with or without the addition of nutrients,[5] or it may be derived directly from a fingerstick sample; b) In the context of this document, whole blood refers primarily to blood derived from a fingerstick.

5 Point-of-Care Coagulation Testing (POC-CT)—General Considerations

Justification for using POC-CT in a given clinical setting involves a careful "needs assessment," which includes the needs of the patient, the provider, the payer, and the institution. The following list includes many of the questions that should be asked before selecting the tests and instruments for each POC-CT setting. Many of these questions are addressed in detail in NCCLS document AST2—*Point-of-Care* In Vitro *Diagnostic (IVD) Testing*.

- **Rationale for Selection of the System:**

– What is the specific clinical need for POC-CT?
– What is the purpose of the test (i.e., to monitor heparin/warfarin therapy)?
– What is the patient population and testing environment?
– Will POC-CT improve patient care/patient outcome?
– How will cost be affected?
– What is the cost benefit ratio?

- **General Administrative Issues:**

– Who will select, purchase, and maintain the system?
– Who is responsible for direction and supervision of testing?
– Who holds the license or certificate for testing?
– How will inventory be controlled?
– How will the test be billed?
– How will the expense of training be incorporated into the test charge?

- **Logistical and Technical Issues:**

– Who will perform the testing?
– Who will train individuals to perform testing?
– What are the specimen requirements?
– How will the method of test ordering be developed?
– How will results be recorded?
– How will results be reported?
– How will results be managed and stored?
– Who is responsible for troubleshooting and assuring availability of a backup procedure?

6 Quality Management: General Considerations for Point-of-Care Coagulation Testing

A quality management system should be implemented to provide consistently reliable results that can be used to guide patient therapy. The basic elements of such a system include a defined organizational structure, standard operating procedures for all aspects of the testing program, periodic training and competency assessment for all test operators, process control procedures (quality control, external proficiency testing, split samples, etc.), incident management, and auditing. (See NCCLS document EP18—*Quality Management of Unit-Use Testing* for further information.)

6.1 Operators, Materials, and Performance of POC-CT

POC-CT should be performed by trained healthcare providers. Before performing the test, the following should be assessed:

- quality control tests have been performed with acceptable results according to the manufacturer's and institutional recommendations;
- disposables are within the expiration date;
- disposables and instruments are devoid of any contaminants (e.g., blood); and
- other specified manufacturer's recommendations have been followed.

6.2 Training

Operators performing point-of-care unit-use tests should have formal training in the systems involved or have worked under the supervision of an experienced laboratorian until they have satisfactorily demonstrated proficiency for each procedure. The degree of training depends upon both the background of the individual who will be performing the testing and the analytical systems being employed (e.g., the complexity of the system, the degree of technique dependence, etc.). When selecting a system, the level of training that is required to implement a new method or instrument should be considered.

Training of individuals who perform the tests should include the following:

- theory of instrument/device/test system;
- specimen collection/preservation/transport;
- instrument calibration;
- instrument maintenance;
- quality control principles and procedures;
- testing procedure;
- sources and degree of error (preanalytic, analytic, and postanalytic); and
- clinical significance.

Sources of training include:

- manufacturer's on-site training and telephone technical assistance;
- local hospital laboratory or commercial laboratory;
- medical technologists or other trained personnel available as consultants; and
- workshops and training seminars.

Evaluating the competency of all testing personnel and ensuring the staff's continuing competency to perform tests and report tests promptly, accurately, and proficiently are essential components of a quality testing system. Individuals must demonstrate competency in performing the procedure, and evidence of this competency must be documented. Competency assessment should be performed annually or/as per institutional policies and procedures. Evaluation of the competency of the staff may include, among other procedures, the following:

- direct observation of routine patient test performance, including patient preparation (if applicable), specimen handling, specimen processing, and testing;
- monitoring the recording and reporting of test results;
- review of intermediate test results or worksheets, QC records, proficiency testing results, and preventive maintenance records;
- direct observation of QC testing;
- direct observation of instrument maintenance and function check performance;
- assessment of test performance through testing of previously analyzed specimens, internal blind testing samples, or external proficiency testing samples;
- assessment of problem-solving skills;
- use of corrective action logs for failed QC; and

- evaluation and documentation of the performance of persons responsible for testing, and providing such documentation to the testing personnel manager.

6.3 Quality Control and Proficiency Testing

The goal of process control is to confirm that all system components are performing as specified by the manufacturer and at a quality level acceptable to the user. System components include the operator, the instrument, the reagents, the sample, and the environment. Various forms of controls test different parts of the process. (For additional procedures for test validation, refer to the most recent version of NCCLS document GP29—*Assessment of Laboratory Tests When Proficiency Testing is Not Available*.)

Process controls should comply with all institutional or jurisdictional requirements. At a minimum, process controls should be performed as specified by the manufacturer. Users may implement additional controls. The types selected should check the components most vulnerable to failure. Periodically, material should be used that verifies all system components at one time under usual testing conditions. The composition and frequency of such testing should be defined by considering the following characteristics:

- variability in storage conditions;
- availability of alternate or simulated testing (i.e., electronic QC);
- duplicate testing;
- ability to utilize split patient samples;
- anticipated failures and likelihood of occurrence;
- available control materials;
- operator experience with the test system;
- institutional experience with the test system;
- the medical impact of the test results; and
- occurrence of improper handling (e.g., dropped device, excess heat).

Users of POC-CT systems are encouraged to refer to NCCLS document EP18—*Quality Management for Unit-Use Testing.*

6.3.1 Quality Control

The manufacturer should develop system-specific QC recommendations that are consistent with the robustness and stability of the test system, its intended use, and with the device's process controls and available QC modalities. When designing a quality control approach, it is important to consider the specific characteristics of a test system. Recommendations should be based on the findings of a hazard analysis, and supported by valid scientific evidence.[a] The manufacturer may provide additional recommendations for corrective action when QC fails. Users of POC-PT systems are encouraged to refer to NCCLS document EP18—*Quality Management for Unit-Use Testing*.

6.3.1.1 Specific Recommendations for Manufacturers of POC-CT

Manufacturers must provide minimum quality control testing recommendations. It is also advisable for the manufacturer to provide practical information for users regarding the types of quality control procedures which may be employed and the value of each system. Manufacturers should address the following:

[a] In the U.S., users of POC-PT systems must work with the local holder of the laboratory license to develop an appropriate QC program. Requirements will vary depending upon the test CLIA (Clinical Laboratory Improvement Amendments) complexity category and relevant local accreditation rules.

- **Target of the quality control material/modality**. Clearly define and communicate to the user the process, analytic procedure, or portion of the assay controlled by each QC material/modality.

- **Quality control material/modality levels**. Ensure that the QC materials/modalities span the medical decision range of the assay and target medically relevant decision points.

- **Tolerances for quality control materials.** Ensure that tolerances for wet quality control materials are relevant in terms of total allowable error. Ranges that are too broad may be incapable of reliably detecting unacceptable levels of imprecision or bias. Account for matrix effects in relating the tolerance ranges to the total allowable error.

  Establish tolerance ranges that provide meaningful quality control without the use of statistical tools (e.g., Westgard rules). Alternatively, incorporate statistical methods in the device software to provide access by nonlaboratory professionals to statistical quality control.

- **Sensitivity of the quality control material/modality to detect analytical problems**. Conduct a hazard analysis to identify potential test system failures. Using valid scientific evidence, demonstrate that the proposed QC protocol is capable of detecting these failures at an acceptable rate. This may be accomplished by experimentally challenging the system (e.g., accelerated degradation of the reagent, etc.) and verifying the ability of the QC method to detect the system failure.

  Identify significant matrix bias. QC testing may be run in parallel with actual patient samples to determine the sensitivity of the QC material to deviations in test system performance or operator error.

6.3.2 Proficiency Testing

Proficiency testing is an important tool for the ongoing validation of adequate test system performance.[b] This should be taken into consideration for instrument users in professional settings. Whenever possible, users of these devices should enroll and regularly participate in proficiency testing programs.

6.4 Result Recording and Reporting

All patient test results should be reported in a timely fashion to the appropriate healthcare provider and recorded in the patient's medical record in a consistent, predictable place so that all members of the healthcare team may access them easily. It is recommended that results are tracked in such a fashion that they can be easily correlated with anticoagulant dose adjustments and changes in other medications. Results may be entered into the laboratory information system (LIS) or clinic records; they may also be part of the general summary of all laboratory tests. Access to results should be password-oriented with graded access to the information when applicable.[c] With sequential testing, healthcare providers should be able to easily review results over time. Normal reference and target therapeutic ranges should be clearly stated to facilitate correct interpretation of patient results. If transcription is the primary method of result recording, periodic auditing should be performed to assess the incidence of transcription errors. The potential for such errors can be significantly reduced through the use of computerized data management systems. These systems typically allow both downloading of results from the analyzer to the data manager and bidirectional interfacing from the data manager to the LIS. A method should be established for rejection-verification of test results before transfer to the LIS. Results of quality control tests and other quality assurance activities must be documented and readily available for regulatory and accreditation purposes. Records of other test-related information (e.g., ordering physician, test operator,

[b] In the U.S., proficiency testing is mandated by CLIA certification.
[c] In the U.S., access to results should comply with HIPPA requirements.

lot numbers, expiration dates for consumables, maintenance, testing difficulties, etc.) must also be maintained. Either paper- or electronic-based systems are acceptable.

7 Monitoring Heparin Therapy

7.1 Introduction

Unfractionated heparin is routinely used in the treatment of thrombosis and thromboembolic complications, because it is instantly effective, immediately reversible, generally well tolerated, and inexpensive. However, bioavailability and anticoagulant effect of heparin vary considerably among normal subjects and patients with different conditions. Thus, frequent monitoring of anticoagulant effect and appropriate dose adjustment are required in patients treated with heparin.[6] Selection of POC-CT systems for the monitoring of heparin anticoagulation should be based on the intended clinical application, i.e., the range of heparin concentrations to be targeted in a particular clinical condition and patient population. Heparin doses may be classified as shown in Table 1. Thus, standard or intermediate-dose heparin therapy is generally used for treatment of low- to moderate-level thrombosis/thrombotic risk, i.e., venous thromboembolism (VTE) (including deep vein thrombosis (DVT) and pulmonary embolism (PE)), hemodialysis, diagnostic (e.g., cardiac catheterization) and interventional cardiology (PCI), interventional radiology (e.g., catheter-directed thrombolytic therapy), long-term extracorporeal support such as extracorporeal membrane oxygenation (ECMO) and ventricular assistance device (VAD), and surgical interventions where thrombotic complications are common (e.g., orthopedic surgery). In contrast, high-dose heparin therapy is generally employed in cardiac surgery involving cardiopulmonary bypass (CPB). All of the available POC-CT systems use whole blood specimens. Test systems vary with regard to specimen volume requirements, activators (e.g., kaolin, celite), and clot detection methods, but have in common the use of "unit" use cartridges, which are discarded after testing. The most commonly used POC-CT for heparin monitoring (which are described below) are the activated clotting time (ACT),[7] activated partial thromboplastin time (APTT),[8] and heparin concentration measurements. For the commonly used test systems, the applicable therapeutic heparin ranges are indicated by the manufacturer.

Table 1. Classification of Heparin Dose Regimens Used in the Prevention and Treatment of Venous and Arterial Thromboembolic Complications

Heparin Dose	Heparin Concentration, U/mL	Clinical Use	Methods for Monitoring
Standard	0.2 - 0.5	Venous thromboembolism	APTT; Heparin Concentration
Intermediate	0.5 - 3.0	Hemodialysis ECMO/VADs Diagnostic Catheterization PCI	ACT; APTT; Heparin Concentration
High	3.0 - 8.0	Cardiac surgery (CPB)	ACT; Heparin Concentration

In patients requiring extended anticoagulant therapy, anticoagulation is changed from heparin to another agent which can be administered more conveniently by mouth, such as warfarin. Warfarin anticoagulant effect is not instantaneous but depends on moderate reduction of plasma levels of vitamin K-dependent procoagulant factors II and X, which takes two to three days. Thus, heparin administration must be continued until the prothrombin time (PT)[9] or its commonly used expression PT-INR (used to monitor warfarin anticoagulation) has been in the desired therapeutic range for two days.[10] During the overlap period the results of tests used to monitor heparin therapy may be prolonged by the effects of warfarin and thus should be interpreted with caution.

7.2 Blood Specimen Collection and Handling

7.2.1 Blood Specimen Type

Arterial or venous blood specimens are frequently used. Whether there are clinically significant differences between arterial and venous blood measurements has not been adequately studied. Preferably, venous specimens should not be obtained from heparin-coated central venous lines or pulmonary artery catheters. Capillary specimens are generally not used with tests that require volumes of blood ≥0.4 mL. Follow the manufacturer's directions for obtaining the correct specimen type.

7.2.2 Blood Specimen Collection

General blood specimen collection and handling procedures should be followed as described in NCCLS documents H3—*Procedures for Collection of Diagnostic Blood Specimens by Venipuncture*; H11—*Procedures for the Collection of Arterial Blood Specimens*; and H4—*Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens.* Specimens may be collected by venipuncture, capillary puncture or from indwelling lines as specified by the POC-CT system manufacturer. Only specimen types for which the performance of the system has been characterized should be used. In obtaining specimens by venipuncture, sterile collection procedures should be used and the manufacturer's instructions regarding collection vehicle (e.g., test tube, syringe, capillary tube) should be followed. For indwelling catheters, the line should be flushed[11] with 5 mL saline; separate, single-use syringes should be used to collect at least 5 mL or 6 dead space volumes of blood (to be discarded) prior to collection of blood specimens for testing, to minimize effects of hemodilution (e.g., crystalloid fluid in line) or heparin in solutions used for flushing indwelling lines. Institutional policies and procedures should be followed.

7.2.3 Blood Specimen Handling and Testing

Free flowing blood specimens may be collected without the use of anticoagulant or they can be drawn into anticoagulant (e.g., citrate), depending on the specifications of the POC-CT system used. Most test systems require native whole blood. Nonanticoagulated blood collected into a plastic syringe should be transferred to the test unit without delay according to the manufacturer's recommendation. Citrated blood specimens should be tested within one hour according to NCCLS document H21—*Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays.*

7.3 POC-CT Systems Used for Monitoring Heparin Therapy

7.3.1 Activated Partial Thromboplastin Time (APTT)

The APTT was first described in 1961 as a global, two-stage coagulation screening test,[8] which is particularly sensitive to deficiencies of or inhibitors to intrinsic phase blood coagulation factors, lupus anticoagulants, and heparin.[8,12,13] An aliquot of citrated, platelet-poor test plasma is incubated with an activator of the coagulation contact system (e.g., kaolin, silica, celite, ellagic acid) for a standard period of time (three to five minutes), calcium chloride is added, and the time required for clot formation is recorded.

7.3.1.1 Description of POC-APTT

The POC-APTT is a one-stage assay based on the same principles as the routine APTT performed in the clinical laboratory (see the current edition of NCCLS document H47—*One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test*). Native or citrated blood is added to a cartridge containing a contact activator such as celite, and phospholipid, and the time required for clot formation is recorded (for citrated blood after addition of calcium chloride). Different activators and phospholipid preparations are used with various POC-APTT systems. Systems vary with regard to

required specimen volume, use of citrate anticoagulant, and method of clot detection. POC-APTT systems are single-use or unit-use systems. With most POC-APTT systems the manufacturer specifies the system's ability to detect changes in heparin and coagulation factor concentration. The most common POC-APTT clinical application is monitoring of low- to intermediate-dose heparin therapy yielding plasma heparin concentrations of 0.2 to 1 U/mL. Some POC-APTT systems may not be suitable for monitoring of anticoagulant effects of target heparin concentrations >1.0 U/mL.

7.3.1.2 Test Performance

Tests should be performed according to the system manufacturer's directions. The correlation between POC-APTT and laboratory-based APTT should be evaluated.

7.3.1.3 Test Result Interpretation and Limitations

Knowledge of a POC-APTT system's ability to detect changes in heparin concentration in the desired therapeutic range is important. Before instituting clinical use of POC-APTT, the user should establish the system normal reference range using blood specimens from at least 20 normal, apparently healthy male and female subjects. There is relatively high variability of both laboratory-based and POC-APTT results in normal subjects and especially in patients on heparin therapy due in part to the current lack of laboratory APTT reagent standardization and variably extensive binding of heparin to endothelial cells and cellular and soluble blood components.[9,12] **It is therefore generally difficult to assess trueness of POC-APTT by comparing individual POC-APTT results with laboratory-based APTT results.** Users must therefore establish normal and therapeutic reference ranges for each test system independently. The therapeutic reference range for each POC-APTT system may be established using normal blood to which therapeutic concentrations of heparin have been added. Alternatively, blood specimens from patients on heparin therapy may be used.[14] Heparin concentrations in those specimens may be determined by anti-Xa, anti-IIa chromogenic assays, protamine sulfate titration, or heparin response measurements. The preanalytic factors affecting POC-APTT test results are largely those affecting the results of laboratory-based APTT (see the current edition of NCCLS document H47—*One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test*).[12,13] Even without anticoagulation therapy, patients with antiphospholipid antibodies (like lupus anticoagulant) may have prolonged POC-APTT test results. The usefulness of POC-APTT in routine monitoring of heparin therapy has been evaluated in only a limited number of studies. Use of the POC-APTT may decrease turnaround time, time for clinical decision making, and time to yield target therapeutic range heparin levels.[15]

7.3.2 Activated Clotting Time (ACT)

The ACT has been used as a POC-CT for high-dose heparin activity monitoring with CPB since its description in 1966.[7] However, more recently, ACT systems have become available which allow monitoring of intermediate dose heparin therapy (0.5 to 3.0 U/mL) in clinical settings such as hemodialysis, intensive care units, diagnostic cardiac catheterization, and PCI.[9,12,16]

7.3.2.1 Description of ACT

Native whole blood is added to a cartridge containing a contact activator, which triggers a clot detection system, and the time in seconds to yield a clot is determined. The ACT is a global coagulation test potentially affected by abnormalities of the intrinsic and common phase of blood coagulation that can be used to measure heparin anticoagulant activity. With ACT or ACT-like systems, a linear relationship between heparin concentrations and clotting times is observed in individual patients over specified heparin concentration ranges. ACT test systems vary with regard to specimen volume and collection requirements, type of contact activator, and clot detection methods. All available ACT tests are single-use or unit-use systems. Some ACT test systems also include a heparin neutralization component, such as

heparinase or protamine, to test for residual heparin following heparin neutralization post-CPB or use of plasma-mixing to assess potential factors other than heparin, such as clotting factor deficiencies or lupus anticoagulants which may prolong the clotting time.

7.3.2.2 Test Performance

Tests should be performed according to the manufacturer's directions.

7.3.2.3 Test Result Interpretation and Limitations

Before instituting use of an ACT test system, the users must establish the normal reference range using blood obtained from at least 20 normal, apparently healthy male and female subjects. Since there is no "standard" ACT against which individual systems can be referenced, it is necessary to establish normal and therapeutic ranges for each system and activator used. ACT systems are designed to achieve linear responsiveness over a specific, desired range of heparin concentrations. Users must select the test system appropriate for the intended clinical application and target heparin ranges (e.g., intermediate-dose heparin therapy in hemodialysis (0.5 to 1.5 U/mL) or PCI (2 to 3 U/mL), or high-dose heparin therapy in cardiac surgery with CPB (3 to 8 U/mL)). It is the responsibility of the manufacturer to specify the range of heparin concentration, which can be reliably measured with a particular ACT system, and assure linear responsiveness of ACT values within the specified range of heparin concentrations.

ACT or ACT-like tests may be frequently affected by a number of preanalytic, patient-related,[17] and clinical[18,19] variables such as the effects of hypothermia and/or hemodilution. The ACT may also be affected by platelet concentration, impaired platelet function, and the effects of certain antiplatelet agents.[20,21] Serine protease inhibitors (e.g., aprotinin) can substantially prolong the ACT by binding and/or inhibiting contact activators, such as celite,[22,23] while ACT systems using kaolin are not affected at low to moderate concentrations of aprotinin.[24] Reductions in coagulation factors secondary to presurgery warfarin therapy,[19] lupus anticoagulants,[25,26] and inherited deficiencies of contact system factors[17] may prolong the ACT and thus may make adequate monitoring of heparin therapy with ACT difficult or impossible.

Analytical variables that should be considered as possible causes for ACT variability are differences among different ACT systems with regard to endpoint detection, automation, deviation from the manufacturer's instructions for storage of cartridges, and conditions such as instrument temperature and humidity.

7.3.3 POC Heparin Concentration Measurements

Heparin concentration may be determined with an automated whole blood POC system based on neutralization of heparin by protamine sulfate (PS) (automated PS titration system).[27,28] Measurement of heparin concentration by POC-PS titration may be particularly useful in patients with suspected heparin resistance[19,29,30] and patients undergoing cardiac surgery to more effectively suppress excessive intravascular coagulation,[31] or when functional tests like the ACT may give inaccurate results due to contact factor deficiencies or lupus anticoagulants.[19]

7.3.3.1 Description of Test

Blood containing heparin is added to cartridges containing tissue thromboplastin reagent and different amounts of PS, and the clotting times are determined. The heparin concentration in blood is calculated by determining the amount of PS causing maximal shortening of the clotting time (equivalent to complete neutralization of heparin) and taking into account the predetermined PS/heparin equivalency.

7.3.3.2 Test Performance

Tests should be performed according to the system manufacturer's directions.

7.3.3.3 Test Result Interpretation and Limitations

Heparin levels determined by this system have been shown to correlate reasonably well with those determined by anti-Xa chromogenic assay in plasma, even in the presence of aprotinin.[19,20] PS titration-based POC-test systems may yield lower heparin levels than laboratory-based anti-Xa or anti-IIa-based systems, particularly with low- and intermediate-dose heparin monitoring (e.g., <1 U/mL).[19] A major potential advantage of heparin concentration monitoring by POC system is related to the fact that the results are less affected by factors such as hemodilution, hypothermia, and pharmacologic agents (e.g., antiplatelet agents, aprotinin), and not at all affected by lupus anticoagulants or inherited deficiencies of contact factors.[19] However, on the other hand, heparin concentration measurements do not allow assessment of anticoagulant effects (intensity of anticoagulation) and may be misleading in certain patients with low levels of AT due to excessive consumption (e.g., DIC or preoperative heparin infusion for several days), and/or decreased production (e.g., liver failure).[30]

7.4 Specific Applications

7.4.1 Cardiac Surgery

High-dose heparin anticoagulation (to yield heparin levels of 3 to 8 U/mL and ACT values between 350 to 800 seconds) is required during cardiac surgery with CPB to prevent clot formation in the extracorporeal circuit and to minimize excessive CPB-related activation of the hemostatic system.[19] There is substantial variability of heparin anticoagulant responses even with high-dose therapy as illustrated by a wide range of heparin response slope values (expressed as the increase in clotting time in seconds per unit of heparin per mL of blood) in patients undergoing cardiac surgery, and this variability seems to be greater than that observed in normal volunteers.[30] This variability in heparin responsiveness is related to substantial variation in the extent of heparin binding to endothelial cells and cellular (e.g., platelets, monocytes, polymorphonuclear leukocytes) and soluble blood components (e.g., AT, fibrinogen, platelet factor 4, Factor VIII).[19] Therefore, it is imperative to monitor heparin closely during cardiac surgery to minimize bleeding and thrombotic complications.

In cardiac surgery with CPB, most heparin monitoring protocols include measuring a preheparin, baseline ACT, administering a weight-based (300 to 400 U/kg) heparin loading bolus, and repeating an ACT every 30 to 60 minutes, to allow further adjusting of the heparin dose by giving additional heparin boluses to achieve and maintain either an ACT within the targeted range (typically 400 to 600 seconds) or maintain heparin concentration within a targeted range (3 to 8 U/mL).[28,32] Alternatively, the initially required heparin dose may be estimated by measuring the *ex vivo* anticoagulant response of the patient's blood to heparin before administering the initial heparin bolus.[28,33] An alternative approach to monitoring anticoagulation during CPB may be achieved by using measurements of heparin concentration in addition to ACT values to maintain a specific target heparin concentration (see Section 7.3.3).

At the end of CPB, heparin must be effectively neutralized to prevent excessive postoperative bleeding. This is usually accomplished by administration of PS, which forms relatively stable complexes with heparin that are cleared from the circulation.[19] The methods used for heparin neutralization by PS will not be discussed here.[19]

7.4.2 Interventional Cardiology/Radiology

Heparin is required to prevent excessive coagulation and thrombus formation during diagnostic catheterizations or PCI. The level of heparin required is based upon the procedure; low dose (0.1 to 1.0

U/mL) during diagnostic cardiology or radiology, and intermediate dose for more aggressive PCI procedures including PTCA, and coronary stent placement (1.0 to 3.0 U/mL). Appropriate monitoring tests, such as the POC-APTT, ACT, or heparin measurement, must be selected based upon the target heparin concentration range.[34,35] With any of these procedures the end user should be aware of potential effects of contrast agents on coagulation measurements.

7.4.3 Intensive Care Units

Heparin is commonly administered in the intensive care unit for prophylaxis and/or treatment of thromboembolic complication. The targeted heparin levels are usually below 1.0 U/mL. The selection of POC test systems for monitoring heparin therapy should be based on the target heparin concentration range. A POC-APTT or ACT system or heparin concentration assay may be used as long as the system has adequate responsiveness to reliably determine anticoagulation intensity within the target range.[36,37]

7.4.4 Hemodialysis

Monitoring of heparin therapy for hemodialysis using target peak concentrations usually not exceeding 1.5 U/mL may be accomplished with an appropriate ACT system, or POC-APTT system, or heparin concentration assay as long as the system has adequate responsiveness to reliably determine anticoagulation intensity within the targeted range.

7.4.5 Standard Intermediate Dose Heparin Therapy (e.g., for venous thromboembolism)

Monitoring of heparin in the treatment of venous thrombosis and pulmonary embolism (target heparin concentration of 0.2 to 0.4 U/mL by PS titration or anti-Xa measurements corresponding to 0.2 to 0.4 U/mL by PS titration)[6,15] is generally performed using laboratory-based APTT but may be performed using a POC-APTT system as appropriate. The normal and therapeutic ranges for each system must be established independently. The correlation between POC-APTT system results and laboratory-based APTT results must be initially established and periodically monitored.

8 Monitoring Warfarin Therapy

8.1 Introduction

An important advancement in oral anticoagulation therapy management has been the development of systems that allow POC performance of the prothrombin time (POC-PT). POC-PT systems measure the clotting time using native whole blood, citrated whole blood, or citrated plasma. The test result is available in a few minutes and is expressed as a PT in seconds, or an international normalized ratio (INR). The latter expression is recommended, because it reduces intersystem variation in test results. POC-PT systems are available for professional use in hospitals, clinics or office settings, and for home use allowing patients to perform their own INR monitoring. Major advantages of POC-PT testing include decreased need for venous access; increased patient and care provider convenience; facilitation of more frequent PT-INR monitoring and warfarin dose adjustment likely resulting in greater time in therapeutic range[38]; more timely, direct, and clear physician/caregiver/patient communication; improved efficacy and safety[39]; and decreased cost of long-term anticoagulant therapy.[40]

8.2 Blood Specimen Collection and Handling

POC-PT systems are typically intended for use with capillary whole blood obtained by a fresh fingerstick. The blood is applied immediately to a test strip or cartridge. The volume of blood required differs with each instrument. The recommended method for acquisition of the blood specimen is described in the package insert of each system. Alternatively, guidelines for specimen collection are available in NCCLS document H4—*Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens.*

Depending on the test system, blood specimens other than capillary blood may be used. The manufacturer is responsible for establishing the suitability of recommended specimen types, whether capillary, citrated, or native venous whole blood or plasma. Only blood specimen types for which the performance of the system has been characterized should be used. When using native venous whole blood, the specimen can be drawn in an anticoagulant-free plastic syringe and rapidly expressed from the syringe before coagulation begins. Since test systems are primarily designed for use of native whole blood, specimen storage is generally not applicable. When using citrated specimens, standard blood specimen collection, processing, and storage recommendations apply (see NCCLS documents H3—*Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture;* H18—*Procedures for the Handling and Processing of Blood Specimens*; and H21—*Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays*) unless otherwise stated by the manufacturer.

8.3 Test Systems Used for Monitoring Warfarin Therapy

8.3.1 PT Test Systems

8.3.1.1 Descriptions of Tests

Different types of technologies are employed in currently available POC-PT test systems. In addition, several systems are also approved for patient self-testing. Each system uses a tissue thromboplastin reagent contained within a disposable test unit. The whole blood or plasma blood specimen is added, and the time to clot formation is measured and converted to a plasma-equivalent PT and/or INR. The method for detection of the endpoint differs from system to system and from that of a conventional laboratory plasma-based PT. When the endpoint is reached, the device software converts the observed time to an INR and/or plasma-equivalent PT. The time at endpoint is converted using a formula established by the manufacturer to make the test result traceable to the reference World Health Organization (WHO) tilt-tube/international reference preparation (IRP) method. This calibration is achieved by simultaneously testing blood specimens with the POC system and with a predefined instrument/thromboplastin combination, traceable to the reference WHO tilt-tube/IRP method. The conversion equation thus obtained is embedded in the device software. Results are customarily displayed on the instrument monitor. Users of POC systems should have a basic understanding of the POC-PT test system and technologies available and the particular system to be used before instituting POC-PT testing.

8.3.1.2 Test Performance

Tests should be performed according to the system manufacturer's directions. The first or second drop of blood is directly applied to a target area on the test unit. The test is initiated immediately and automatically after specimen application. The correlation between the POC-PT/POC-INR and the laboratory method should be known.

8.3.1.3 Test Result Interpretation and Limitations

The systems are calibrated to determine a PT/INR from whole blood within a defined range of hematocrits and platelet concentrations as defined by the manufacturer. The manufacturer also identifies other variables impacting on the trueness and precision of test results.

Use of the INR is essential for correct interpretation of PT results and proper management of oral anticoagulation. INR corrects for differences in thromboplastin reagent sensitivity to warfarin-induced reductions in vitamin K-dependent, procoagulant coagulation factors. The INR is a product of the WHO standardization scheme through which different thromboplastin reagents are calibrated against an IRP thromboplastin. The WHO reference method widely used for calibration of commercial thromboplastin preparations consists of simultaneously testing normal plasmas and plasmas from warfarin-anticoagulated

patients with the IRP and a specific thromboplastin to be used in PT testing. The new thromboplastin is assigned an international sensitivity index (ISI) based on its comparison to the IRP. The ISI is then used to compute the INR results. Since ISI values of thromboplastins vary with use of different clot timers, manufacturers of thromboplastins provide ISI values for a specific thromboplastin/clot timer combination.

An identical standardization approach cannot be used with POC systems, since the WHO reference procedure determines PT results on citrated plasma samples using a manual tilt-tube method. POC instruments (with their own specific thromboplastin reagents) are generally calibrated by comparing POC test results to those obtained with a predefined thromboplastin/clot timer combination (i.e., secondary reference) that is traceable to the WHO IRP/tilt-tube method.

INR standardization considerably improves comparability of results obtained with different test systems. However, it does not correct for all potential variables. This is true for both laboratory-based and POC-PT test systems. Moreover, poor correlation of INRs obtained with highly sensitive (low-ISI) thromboplastins and less sensitive (high-ISI) thromboplastins may be observed.

The INR system is very useful but imperfect, and clinically important discrepancies of INR are often observed among different laboratory-based PT test systems as well as point-of-care test systems. In a study of laboratory-based PT systems, a 20% INR nonagreement was noted using 12 different reagent/instrument combinations which represented only a fraction of the 300 possible reagent/instrument combinations.[41] Similar results were reported in another recent study of variability of laboratory-based INR.[42] Similarly, extensive INR variability has been reported for different POC-PT systems.[43,44] The likelihood of observing clinically important system differences increases as the INR rises above 3.0. Clinicians and laboratorians must recognize INR differences that have clinical decision impact. In this regard, others[45] noted that when looking at repeated measurements, statistically there is an equivalence of INRs that are within 0.4 at a target INR of 2.5 and 0.7 at a target INR of 3.5. In a large comparison study,[46] the percentage of INR agreement between a POC system and a reference laboratory system was similar to that observed between a local hospital laboratory and the reference laboratory.

When attempting to establish the trueness of a POC system, the required comparative data analysis must include traditional correlation analysis, mean versus difference plots, and assessment of the incidence of clinically important INR differences.

Results exceeding an INR of 5.0 generally have reduced trueness, precision, and linearity, both in POC- and laboratory-based PT testing. These results should be interpreted accordingly. Appreciation of the general agreement between INR results obtained at POC and different laboratory-based systems is essential for optimal patient management. Although there has been considerable concern about the reliability and safety of POC-PT testing (particularly when performed by patients themselves), published evidence[47] seems to support the notion that POC-PT testing is as reliable as laboratory-based testing. Furthermore, it has been shown in a number of comparative studies that percent time in therapeutic range (TTR) may be considerably increased in patients monitored by POC-PT testing as compared to patients monitored by laboratory-based PT testing, possibly in part related to more frequent testing in POC-PT monitored patients.[47] It would clearly be desirable to have definitive evidence that monitoring by POC-PT testing is as good or better than laboratory-based PT monitoring in terms of long-term outcome (i.e., prevention of recurrent thromboembolic complications and minimization of warfarin side effects; in particular, serious abnormal bleeding). However, the cost of such studies, which would require enrollment of tens of thousands of patients, is likely to be prohibitive.

8.4 Specific Applications

8.4.1 Healthcare Provider Use

POC-PT tests are used in a variety of outpatient and inpatient settings, primarily for monitoring oral anticoagulant therapy. These settings include emergency rooms, outpatient clinics, physicians' offices, hospital wards, surgical suites, and intensive care units.

POC-PT tests offer several advantages over conventional laboratory tests such as:

- ease of use (systems may be operated by trained, nonlaboratory healthcare providers);
- suitability for various blood or plasma specimen types;
- rapid availability of results;
- ability to immediately repeat testing if initial results are questionable; and
- convenience for the patient in terms of access to testing.

8.4.2 Patient Self-Testing (PST)

POC-PT systems intended for use in the home environment are designed to perform reliably in multiple settings and under varying conditions of temperature, humidity, light, and physical handling. These instruments provide simple prompts to the user and generally require minimal maintenance and calibration. They are lightweight and highly portable.

8.4.2.1 Patient Selection

Not all patients requiring oral anticoagulant therapy are candidates for PST. Careful selection of patients is essential. Criteria for selection of patients for PST include:

- adequate understanding of indication for and potential benefits and risks of warfarin anticoagulation;
- physical/mental ability to perform PST;
- willingness to perform PST;
- willingness to comply with requirements for procedures, recording of QC data and timely communication with caregiver in case of test system malfunction or out-of-range QC results;
- history of compliance with medical recommendations; and
- adequate insurance coverage for PST or willingness and ability for self-pay.

8.4.2.2 Training

Participants in a PST program require unique and comprehensive training beyond that traditionally required for professional users of POC-CT systems. POC-CT systems which are intended to be used for PST must have an accompanying manufacturer-recommended training guideline that professionals can reference when selecting and training PST candidates. A proper training program should encompass the following categories:

- Basic disease and anticoagulation information
  - — indication for and duration of anticoagulation therapy;
  - — mechanism of warfarin anticoagulant effect;
  - — prothrombin time and INR;
  - — desired therapeutic INR range;
  - — rationale for monitoring;

- side effects/complications of warfarin anticoagulation;
- impact of diet, drugs, illness, liver function, etc., on INR; and
- relationship between antithrombolic efficacy and bleeding complications.

- Blood collection technique
  - operation of device for fingerstick;
  - fingerstick puncture and aseptic technique;
  - storage, handling, and disposal of supplies and contaminated materials; and
  - care of device.

- Performance of POC-PT test
  - preparation for testing;
  - purpose, and performance of quality control procedures; and
  - storage, handling of test system and cartridges, and disposal of supplies and contaminated material.

- Data management and transmission of results to healthcare provider
  - recording and reporting of results;
  - troubleshooting system errors;
  - maintaining QC data; and
  - communicating with healthcare provider (indication of mechanism - telephone, fax, e-mail).

8.4.2.3 Quality Control Management for PST

Patient self-testers should be instructed regarding the specific manufacturer's guidelines for quality control and quality assurance. Manufacturers should provide written quality control recommendations, which are consistent with the guidelines found in Section 6. Patient training before starting PST should include details of the required quality control procedures. The healthcare professional responsible for the patient's care should document routine verification of patient compliance with quality control requirements. The healthcare provider should additionally verify the patient's technique through direct observation, at regular intervals. Split-sample testing should also be performed, according to an established schedule, to verify that the relationship between the patient's device and the clinical laboratory assay is unchanged and to ensure continued acceptable performance of the patient's device.

8.5 Result Recording and Reporting

The optimal use of POC-CT for patient self-testing requires that the patient effectively communicate reliable test results to the healthcare provider. Reliability of results is determined not only by the performance of the test system but also by the user's testing proficiency, and the patient's compliance in terms of quality control and maintenance of the instrument.

References

[1] ISO. *International vocabulary of basic and general terms in metrology*. Geneva*:* International Organization for Standardization; 1993.

[2] ISO. *Statistics—Vocabulary and symbols – Part 1: Probability and general statistical terms.* ISO 3534-1. Geneva: International Organization for Standardization; 1993.

[3] *Federal Register*. Rules and Regulations; Part 493, Subpart K, Subsection 493.1218 (b) (2):7166. February 28, 1992.

[4] ISO. *Quality management systems – Fundamentals and vocabulary*. ISO 9000. Geneva: International Organization for Standardization; 2000.

[5] WHO. Expert Committee on Biological Standardization. *Glossary of Terms for Biological Substances Used for Texts of the Requirements*. WHO unpublished document BS/95.1793. Geneva: World Health Organization; 1995.

[6] Hirsh J, Anand SS, Halperin JL, Fuster V. Guide to anticoagulant therapy: Heparin. *Circulation*. 2001;103:2994-3018.

[7] Hattersley PG. Activated coagulation time of whole blood. *JAMA*. 1966;196:436-440.

[8] Proctor RR, Rapaport SI. The partial thromboplastin time with Kaolin. A simple screening test for the first stage plasma clotting factor deficiencies. *Am J Clin Pathol.* 1961;36:212-219.

[9] Guick AJ. The coagulation defect in sweet clover disease and in hemorrhagic chick disease of dietary origin: A consideration of the source of prothrombin. *Am J Physiol.* 1937;118:260-265.

[10] Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: Mechanism of action, clinical effectiveness and optimal therapeutic range. *Chest*. 2001;119:8S-21S;1998;114:445S-469S.

[11] Laxson CJ, Titler MG. Drawing coagulation studies from arterial lines: An integrative literature review. *Am J Crit Care*. 1994;1:16-24.

[12] Olson JD, Arkin CF, Brandt JT, et al. College of American Pathologists Conference XXI on Laboratory Monitoring of Anticoagulant Therapy. Laboratory monitoring of unfractionated heparin therapy. *Arch Pathol Lab Med*. 1998;122:782-798.

[13] Bajaj SP, Joist JH. New insights into how blood clots: Implications for the use of APTT and PT as coagulation screening tests and in monitoring of anticoagulant therapy. *Sem Thromb Hemost*. 1999;25:407-418.

[14] Brill-Edwards P, Ginsberg JS, Johnston M, Hirsh J. Establishing a therapeutic range for heparin therapy. *Ann Intern Med*. 1993;119:104-109.

[15] Becker RC, Cyr J, Corrao JM, Ball SP. Bedside coagulation monitoring in heparin treated patients with active thromboembolic disease: A coronary care unit experience. *Am Heart J.* 1994;120:719-723.

[16] Zucker ML, LaDuca FM. Activated clotting time: How to select the right assay for the right clinical application. *Clin Lab News*. 2002:10-12.

[17] Moorman RM, Reynolds DS, Comunale ME. Management of cardiopulmonary bypass in a patient with congenital factor XII deficiency. *J Cardiothor Vasc Anesthesia*. 1993;7:452-454.

[18] Despotis GJ, Summerfield AL, Joist JH, et al. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. *J Thorac Cardiovasc Surg*. 1994;108:1076-1082.

[19] Despotis GJ, Gravlee G, Filos KS, Levy JH. Anticoagulation monitoring during cardiac surgery: A review of current and emerging techniques. *Anesthesiology.* 1999;91:1122-1151.

[20] The EPILOG Investigators: Platelet glycoprotein IIb/IIIa receptor blockade and low dose heparin during percutaneous coronary revascularization. *NEJM*. 1997;336:1689-1696.

[21] Amar T, Scudder L, Coller B. *In vitro* effects of platelet glycoprotein IIb/IIIa receptor antagonist c7E3 Fab on the activated clotting time. *Circulation*. 1997;95:614-614.

[22] Feindt P, Volkmer I, Seijfert U, et al. Activated clotting time anticoagulation, use of heparin and thrombin activation during extracorporeal circulation: Changes under aprotinin therapy. *Thorac Cardiovasc Surg*. 1993;41:9-15.

[23] Hunt BS, Segal HC, Yacoub M. Guidelines for monitoring heparin by the activated clotting time when aprotinin is used during cardiopulmonary bypass. (Letter). *J Thorac Cardiovasc Surg*. 1992;104:211-212.

[24] Despotis GJ, Joist JH, Joiner-Maier D, et al. Effect of aprotinin on activated clotting time, whole blood and plasma heparin measurements. *Ann Thorac Surg*. 1995;59:106-111.

[25] Sheikh F, Lechowicz A, Seflur R, et al. Recognition and management of patients with antiphospholipid antibody syndrome undergoing cardiac surgery. *J Cardiothor Vasc Anesthesia*. 1997;11:764-766.

[26] Ducart AR, Collard EL, Osselaer JC, et al. Management of anticoagulation during cardiopulmonary bypass in a patient with a circulating lupus anticoagulant. *J Cardiothor Vasc Anesthesia*. 1997;11:878-879.

[27] Jobes DR, Schwartz AJ, Ellisson N, et al. Monitoring heparin anticoagulation and its neutralization. *Am Thorac Surg*. 1980;31:161-166.

[28] Gravlee GP, Hadon WS, Rothberger HK, et al. Heparin dosing and monitoring for cardiopulmonary bypass: A comparison of techniques with measurement of subclinical plasma coagulation. *J Thorac Cardiovasc Surg*. 1990;99:518-527.

[29] Levine MN, Hirsh J, Gent M, et al. A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. *Arch Intern Med*. 1996;154:49-56.

[30] Despotis GJ, Levine V, Joist JH, et al. Antithrombin III during cardiac surgery: Effect on response of activated clotting time to heparin and relationship to markers of hemostatic activation. *Anesth Analg*. 1997;85(3):498-506.

[31] Despotis GJ, Joist JH, Hogue CW Jr., et al. More effective suppression of hemostatic system activation in patients undergoing cardiac surgery by heparin dosing based on heparin blood concentrations rather than ACT. *Thromb Haemostasis*. 1996;76(6):902-908.

[32] Bull B, Korpman R, Huse W, Briggs B. Heparin therapy during extracorporeal circulation. I. Problems inherent in existing heparin protocols. *J Thorac Cardiovasc Surg*. 1975:69;674-684.

[33] Bull B, Huse W, Brauer F, Korpman R. Heparin therapy during extracorporeal circulation. II. The use of the dose-response curve to individualize heparin and protamine dose. heparin protocols. *J Thorac Cardiovasc Surg*. 1975;69:685-689.

[34] Ogilby J, Kopelman H, Klein L, Agarwal J. Adequate heparinization during PTCA: Assessment using activated clotting times. *Cath and Cardiovasc Diag.* 1989:18;206-209.

[35] Chew D, Bhatt D, Lincoff M, et. al. Defining activated clotting time during percutaneous coronary intervention. *Circulation*. 2001;103:961-966.

[36] Blumenthal R, Carter A, Resar J, et al. Comparison of bedside and hospital laboratory coagulation studies during and after coronary intervention. *Cath and Cardiovasc Diag.* 1995;35:9-17.

[37] Siskin G, Reiner E, Stainken B, et al. Activated clotting time as a screening test prior to catheter-based cardiovascular procedures. *Cath and Cardiovasc Diag.* 2001;54:191-195.

[38] Samsa GP, Matchar DB. Relationship between test frequency and outcomes of anticoagulation: A literature review and commentary with implications for the design of randomized trials of patient self-management. *J Thrombosis Thrombolysis.* 2000;9:283-292.

[39] Ansell J, Hirsch J, Dalen J, et al. Managing oral anticoagulant therapy. *Chest.* 2001;119-22S-382.

[40] Muller E, Bergemann R, GELIA Study Group. Economic analysis of bleeding and thromboembolic sequelae after heart valve replacement (GELIA 7). *Euro Heart J.* 2001;3(Suppl Q):Q65-Q69.

[41] McGlasson DL. A comparison of INR after local calibration of thromboplastin international sensitivity indexes. *Clin Lab Sci.* 2002:15;91-95.

[42] Jacobson AK, Ruybalid RL, Johnston M, Westengard J. Significant variation in the reporting of prothrombin time results despite utilization of the INR method of reporting. *Circulation.* 1999;100:I-620.

[43] Jacobson AK, Peterson M, Gunneman T, et al. Magnitude of INR variation attributable to differences between point-of-care testing devices. *J Am College of Cardiology.* 2002:39:5, 234A.

[44] Gosselin R, Owings JT, White RH, et al. A comparison of point-of-care instruments designed for monitoring oral anticoagulation with standard laboratory methods. *Thromb Haemostas.* 2002;83:698-703.

[45] Lassen JF, Brandslund I, Antonsen S, et al. International normalized ratio for prothrombin times in patients taking oral anticoagulants: Critical difference and probability of significant change in consecutive measurements. *Clin Chem*. 1995;41:444-447.

[46] Oral Anticoagulation Monitoring Study Group. Point-of-care prothrombin time measurement for professional and patient self-testing use. *Am J Clin Path*. 2001;115:288-296.

[47] Ansel J, Hirsh J, Dalen J, et al. Managing oral anticoagulant therapy. *Chest.* 2001;22S-38S.

NCCLS consensus procedures include an appeals process that is described in detail in Section 8 of the Administrative Procedures. For further information, contact the Executive Offices or visit our website at www.nccls.org.

Summary of Delegate Comments and Subcommittee Responses

H49-P: *Point-of-Care Monitoring of Anticoagulation Therapy; Proposed Guideline*

General

1. This is a valuable document for anyone setting up a POC-CT laboratory. Because it is a "global" document, in some areas it may be vague and excessively general.

- **The subcommittee appreciates the input.**

2. This well-scoped document forms a foundation for more specific guideline(s) for the rapidly diversifying field of POC coagulation.

- **The subcommittee appreciates the positive comment.**

3. This is an important document. A few small comments: Since this is about "Point of Care," I wish the authors would use only THAT term in the document. We need standardization on this term, and to continue the habit of "also referred to as ..." is not helping. I noted this specifically on pages vii,1, and 3.

- **The phrase "also referred to as near-patient testing or bedside testing" has been deleted from page 1. However, the phrase has been retained in the Abstract and the Definitions. POC is used exclusively throughout the rest of the text without mention of the alternative terms. The other terms were retained in the Abstract and Definitions, since this document will be read by others throughout the world where such terms are in common use, and the subcommittee believes it is reasonable to indicate for such readers (especially in the definition) that POC indicates the same process as the other terms denote.**

Section 4, Definitions (Formerly Section 3)

4. "Sample" definition – the last word of the 1st sentence should be "test" instead of "rest."

- **The text has been corrected.**

5. Add "native" and "tilt-tube" to the list of definitions.

- **The suggested definitions have been added to the document.**

Section 6.2, Training (Formerly Section 5.2)

6. Calibrations need to be added to the list of training for users.

- **Instrument calibration has been added to the training list for users.**

7. Evaluating competency should include the use of corrective action logs for failed QC.

- **The use of corrective action logs for failed QC has been added to Section 6.2.**

8. At the top of Page 7 – "medical technologists or other trained personnel available as part-time consultants." Why "part-time"?

- **The term "part-time" has been deleted.**

Section 6.3.1, Quality Control (Formerly Section 5.3.1)

9. Sensitivity of quality control to detect analytical problems should include recommendations of what to do when QC fails.

- **The following text has been added: "The manufacturer may provide additional recommendations for corrective action when QC fails."**

Section 6.3.2, Proficiency Testing (Formerly Section 5.3.2)

10. Proficiency testing is also mandated by CLIA certification; since many nonlaboratory folks are liable to use this document, this should be mentioned.

- **The text has been revised to include that proficiency testing is mandated by CLIA.**

Section 6.4, Result Recording and Reporting (Formerly Section 5.4)

11. A record of expiry dates for consumables should also be kept.

- **The recording of expiration dates for consumables has been added to the text.**

12. Confidentiality has worldwide importance and should be more emphasized with password-oriented, graded access to the information system when applicable.

- **The following text has been added: "Access to results should be password-oriented with graded access to the information when applicable."**

Section 7.2.3, Blood Specimen Handling and Testing (Formerly Section 6.2.3)

13. A statement should be included about "free flowing blood collection."

- **The text has been revised as suggested.**

Section 7.3.1.3, Test Result Interpretation and Limitations (Formerly Section 6.3.1.3)

14. A statement about the effect of phospholipid antibodies on POC-APTT results may be needed.

- **The following text has been added: "Even without anticoagulation therapy, patients with antiphospholipid antibodies (like lupus anticoagulant) may have prolonged POC-APTT test results."**

15. The lack of comparability between laboratory aPTT and POC-CT aPTT should be boldfaced or italicized because of its importance.

- **The text has been boldfaced as suggested.**

Section 7.3.2.1, Description of ACT (Formerly Section 6.3.2.1)

16. "Non-anticoagulated blood" is an ambiguous term, especially if the ACT is used to monitor heparin therapy. Anticoagulant might be present, but it is not added to the specimen/sample after the blood is withdrawn from the patient. This issue should be clarified.

- **The phrase "non-anticoagulated" has been replaced by "native whole."**

Section 7.4.1, Cardiac Surgery (Formerly Section 6.4.1)

17. "The methods used for heparin neutralization by PS will not be discussed here." A reference would be nice.

- **A reference has been added to the end of Section 7.4.1 as suggested.**

Section 7.4.2, Interventional Cardiology/Radiology (Formerly 6.4.2)

18. The potential effects of contrast agents on coagulation measurement should be considered. It is unclear if this is a recommendation to the end user or the manufacturer.

- **The text has been revised for clarification. The following phrase has been added to the last sentence: "…end user should be aware of…"**

Section 8.1, Introduction (Formerly Section 7.1)

19. "Non-anticoagulated (native) whole blood." "Native" should be defined.

- **The term "non-anticoagulated" has been replaced with "native." The term "native" has been added to the definitions.**

Section 8.2, Blood Specimen Collection and Handling (Formerly Section 7.2)

20. "Non-anticoagulated" recurs. It's an issue with *in vivo* vs *in vitro* anticoagulation as above.

- **The term "non-anticoagulated" has been replaced with "native."**

Section 8.3.1.1, Description of Tests (Formerly Section 7.3.1.1)

21. The term "tilt-tube" should be defined.

- **The suggested term has been added to the definitions.**

Section 8.3.1.3, Test Result Interpretation and Limitations (Formerly Section 7.3.1.3)

22. The term "tilt-tube" should be defined.

- **The suggested term has been added to the definitions.**

23. Some of the commentary concerning the lack of comparability, "normalization" or "harmonization" of the laboratory and POC-CT INR should be in bold or italics because of the importance of this issue. Because the PT ratio is multiplied by the ISI power, differences between the laboratory and POC-CT PT ratios will be magnified (vs. mere factoring by the ISI if it were not a power).

- **The text has been boldfaced as suggested.**

Section 8.4.2.2, Training (Formerly Section 7.4.2.2)

24. Why would anyone consider it important to train a patient in "mechanism of warfarin anticoagulant effect" as part of teaching them how to do self-testing? And, in that same section, "impact of diet, drugs, illness, liver function, etc., on INR" - no patient is going to know their liver function. Why not say "laboratory test results"?

- **Education of the patient (who does self-testing) about mechanism of action of warfarin, or liver function, drug interactions, etc., does not imply that detailed, basic science education is provided, but only the bare essentials. For example: warfarin mechanism of action means that warfarin interferes with the ability of the blood to form a clot. It does not "thin out" the blood. The patient must understand that drugs can interact with warfarin (mechanism is not necessary), and thus be alert to tell his/her physician anytime a drug is initiated or discontinued. We realize that patients will not know their liver function, but to understand that impairment of liver function can effect the INR (e.g., too much alcohol intake) is important. We strongly believe that an educated patient is best able to deal with the vicissitudes of INR monitoring. This rudimentary education is really basic to all anticoagulation therapy.**

NOTES

The Quality System Approach

NCCLS subscribes to a quality system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents through a gap analysis. The approach is based on the model presented in the most current edition of NCCLS HS1—*A Quality System Model for Health Care.* The quality system approach applies a core set of "quality system essentials (QSEs)," basic to any organization, to all operations in any healthcare service's path of workflow. The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The quality system essentials (QSEs) are:

Documents & Records	Equipment	Information Management	Process Improvement
Organization	Purchasing & Inventory	Occurrence Management	Service & Satisfaction
Personnel	Process Control	Assessment	Facilities & Safety

H49-A addresses the quality system essentials (QSEs) indicated by an "X." For a description of the other NCCLS documents listed in the grid, please refer to the Related NCCLS Publications section on the following page.

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessment	Process Improvement	Service & Satisfaction	Facilities & Safety
					X AST2 EP18				GP29		

Adapted from NCCLS document HS1—*A Quality System Model for Health Care*.

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, GP26-A2 defines a clinical laboratory path of workflow which consists of three sequential processes: preanalytic, analytic, and postanalytic. All clinical laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

H49-A addresses the clinical laboratory path of workflow steps indicated by an "X." For a description of the other NCCLS documents listed in the grid, please refer to the Related NCCLS Publications section on the following page.

Preanalytic					**Analytic**		**Postanalytic**	
Patient Assessment	Test Request	Specimen Collection	Specimen Transport	Specimen Receipt	Testing Review	Laboratory Interpretation	Results Report	Post-test Specimen Management
X		X H3 H4 H21			X H47		X	

Adapted from NCCLS document HS1—*A Quality System Model for Health Care*.

Related NCCLS Publications*

AST2-A **Point-of-Care *In Vitro* Diagnostic (IVD) Testing; Approved Guideline (1999).** This document contains guidelines for users of *in vitro* diagnostic (IVD) devices outside the clinical laboratory to produce reliable results comparable to those obtained in the clinical laboratory.

EP18-A **Quality Management for Unit-Use Testing; Approved Guideline (2002).** This guideline recommends a quality management system for unit-use devices that will aid in the identification, understanding, and management of sources of error and help to ensure correct results. It is targeted for those involved in the supervision of laboratory-testing quality management, and it addresses issues related to specimen collection through reporting of test results.

GP29-A **Assessment of Laboratory Tests When Proficiency Testing is Not Available; Approved Guideline (2002).** This document offers methods to assess test performance when proficiency testing (PT) is not available; these methods include examples with statistical analyses. This document is intended for use by laboratory managers and testing personnel in traditional clinical laboratories as well as in point-of-care and bedside testing environments.

H3-A5 **Procedure for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Fifth Edition (2003).** This document provides procedures for the collection of diagnostic specimens by venipuncture, including line draws, blood culture collection, and venipuncture in children. It also includes recommendations on order of draw.

H4-A5 **Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens; Approved Standard—Fifth Edition (2004).** This document provides a technique for the collection of diagnostic blood specimens by skin puncture, including recommendations for collection sites and specimen handling and identification. Specifications for disposable devices used to collect, process, and transfer diagnostic blood specimens obtained by skin puncture are also included.

H21-A4 **Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays; Approved Guideline—Fourth Edition (2003).** This document provides procedures for collecting, transporting, and storing blood; processing blood specimens; storage of plasma for coagulation testing; and general recommendations for performing the tests.

H47-A **One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test; Approved Guideline (1996).** This document provides guidelines for performing the PT and APTT tests in the clinical laboratory, for reporting results, and for identifying sources of error.

* Proposed- and tentative-level documents are being advanced through the NCCLS consensus process; therefore, readers should refer to the most recent editions.

NOTES

NOTES

NOTES

NOTES

Active Membership
(as of 1 July 2004)

Sustaining Members

Abbott Laboratories
American Association for Clinical Chemistry
Bayer Corporation
BD
Beckman Coulter, Inc.
bioMérieux, Inc.
CLMA
College of American Pathologists
GlaxoSmithKline
Ortho-Clinical Diagnostics, Inc.
Pfizer Inc
Roche Diagnostics, Inc.

Professional Members

American Academy of Family Physicians
American Association for Clinical Chemistry
American Association for Respiratory Care
American Chemical Society
American Medical Technologists
American Society for Clinical Laboratory Science
American Society for Microbiology
American Society of Hematology
American Type Culture Collection, Inc.
Asociacion Mexicana de Bioquimica Clinica A.C.
Assn. of Public Health Laboratories
Assoc. Micro. Clinici Italiani-A.M.C.L.I.
British Society for Antimicrobial Chemotherapy
Canadian Society for Medical Laboratory Science - Société Canadienne de Science de Laboratoire Médical
Canadian Standards Association
Clinical Laboratory Management Association
COLA
College of American Pathologists
College of Medical Laboratory Technologists of Ontario
College of Physicians and Surgeons of Saskatchewan
ESCMID
International Council for Standardization in Haematology
International Federation of Biomedical Laboratory Science
International Federation of Clinical Chemistry
Italian Society of Clinical Biochemistry and Clinical Molecular Biology
Japan Society of Clinical Chemistry
Japanese Committee for Clinical Laboratory Standards
Joint Commission on Accreditation of Healthcare Organizations
National Academy of Clinical Biochemistry
National Association of Testing Authorities - Australia
National Society for Histotechnology, Inc.
New Zealand Association of Phlebotomy
Ontario Medical Association Quality Management Program-Laboratory Service
RCPA Quality Assurance Programs PTY Limited
Sociedad Espanola de Bioquimica Clinica y Patologia Molecular
Sociedade Brasileira de Analises Clinicas
Taiwanese Committee for Clinical Laboratory Standards (TCCLS)
Turkish Society of Microbiology

Government Members

Armed Forces Institute of Pathology
Association of Public Health Laboratories
BC Centre for Disease Control
Caribbean Epidemiology Centre
Centers for Disease Control and Prevention
Centers for Medicare & Medicaid Services
Centers for Medicare & Medicaid Services/CLIA Program
Chinese Committee for Clinical Laboratory Standards
Commonwealth of Pennsylvania Bureau of Laboratories
Department of Veterans Affairs
Deutsches Institut für Normung (DIN)
FDA Center for Devices and Radiological Health
FDA Center for Veterinary Medicine
FDA Division of Anti-Infective Drug Products
Iowa State Hygienic Laboratory
Massachusetts Department of Public Health Laboratories
National Center of Infectious and Parasitic Diseases (Bulgaria)
National Health Laboratory Service (South Africa)
National Institute of Standards and Technology
National Pathology Accreditation Advisory Council (Australia)
New York State Department of Health
Ontario Ministry of Health
Pennsylvania Dept. of Health
Saskatchewan Health-Provincial Laboratory
Scientific Institute of Public Health; Belgium Ministry of Social Affairs, Public Health and the Environment
Swedish Institute for Infectious Disease Control

Industry Members

AB Biodisk
Abbott Laboratories
Abbott Diabetes Care
Acrometrix Corporation
Advancis Pharmaceutical Corporation
Affymetrix, Inc.
Alifax S.P.A.
Ammirati Regulatory Consulting
Anna Longwell, PC
A/S ROSCO
AstraZeneca Pharmaceuticals
Aventis
Axis-Shield POC AS
Bayer Corporation - Elkhart, IN
Bayer Corporation - Tarrytown, NY
Bayer Corporation - West Haven, CT
BD
BD Consumer Products
BD Diagnostic Systems
BD Thailand Ltd.
BD VACUTAINER Systems
Beckman Coulter, Inc.
Beckman Coulter K.K. (Japan)
Bio-Development SRL
Bio-Inova Life Sciences International
Biomedia Laboratories SDN BHD
bioMérieux, Inc. (MO)
Biometrology Consultants
Bio-Rad Laboratories, Inc.
Bio-Rad Laboratories, Inc. – France
Bio-Rad Laboratories, Inc. – Plano, TX
BioVeris Corporation
Blaine Healthcare Associates, Inc.
Bristol-Myers Squibb Company
Canadian External Quality Assessment Laboratory
Cepheid
Chen & Chen, LLC
Chiron Corporation
ChromaVision Medical Systems, Inc.
Clinical Micro Sensors
The Clinical Microbiology Institute
Cognigen
CONOSCO
Copan Diagnostics Inc.
Cosmetic Ingredient Review
Cubist Pharmaceuticals
Dade Behring Inc. - Cupertino, CA
Dade Behring Inc. - Deerfield, IL
Dade Behring Inc. - Glasgow, DE
Dade Behring Inc. - Marburg, Germany
Dade Behring Inc. - Sacramento, CA
David G. Rhoads Associates, Inc.
Diagnostic Products Corporation
Digene Corporation
Eiken Chemical Company, Ltd.
Elanco Animal Health
Electa Lab s.r.l.
Enterprise Analysis Corporation
EXPERTech Associates, Inc.
F. Hoffman-La Roche AG
Fort Dodge Animal Health
Gen-Probe
GenVault
GlaxoSmithKline
Greiner Bio-One Inc.
Immunicon Corporation
ImmunoSite, Inc.
Instrumentation Laboratory
International Technidyne Corporation
I-STAT Corporation
Johnson and Johnson Pharmaceutical Research and Development, L.L.C.
K.C.J. Enterprises
LAB-Interlink, Inc.
LifeScan, Inc. (a Johnson & Johnson Company)
LUZ, Inc.
Machaon Diagnostics
Medical Device Consultants, Inc.
Merck & Company, Inc.
Minigrip/Zip-Pak
mvi Sciences (MA)
National Pathology Accreditation Advisory Council (Australia)
Nippon Becton Dickinson Co., Ltd.
Nissui Pharmaceutical Co., Ltd.
Norfolk Associates, Inc.
Novartis Pharmaceuticals Corporation
Olympus America, Inc.
Ortho-Clinical Diagnostics, Inc. (Rochester, NY)
Ortho-McNeil Pharmaceutical (Raritan, NJ)
Oxoid Inc.
Paratek Pharmaceuticals
Pfizer Animal Health
Pfizer Inc
Pfizer Italia Srl
Powers Consulting Services
Premier Inc.
Procter & Gamble Pharmaceuticals, Inc.
QSE Consulting
Quintiles, Inc.
Radiometer America, Inc.
Radiometer Medical A/S
Replidyne
Roche Diagnostics GmbH
Roche Diagnostics, Inc.
Roche Laboratories (Div. Hoffmann-La Roche Inc.)
Sarstedt, Inc.
Schering Corporation
Schleicher & Schuell, Inc.
Second Opinion
Seraphim Life Sciences Consulting LLC
SFBC Anapharm
Streck Laboratories, Inc.
SYN X Pharma Inc.
Sysmex Corporation (Japan)
Sysmex Corporation (Long Grove, IL)
TheraDoc
Theravance Inc.
THYMED GmbH
Transasia Engineers
Trek Diagnostic Systems, Inc.
Tyco Kendall Healthcare
Vetoquinol S.A.
Vicuron Pharmaceuticals Inc.
Vysis, Inc.
Wyeth Research
XDX, Inc.
YD Consultant
YD Diagnostics (Seoul, Korea)

Trade Associations

AdvaMed
Japan Association of Clinical Reagents Industries (Tokyo, Japan)

Associate Active Members

Academisch Ziekenhuis -VUB (Belgium)
Alfred I. duPont Hospital for Children (DE)
Allina Health System (MN)
American University of Beirut Medical Center (NY)
Anne Arundel Medical Center (MD)
Antwerp University Hospital (Belgium)
Arkansas Department of Health
ARUP at University Hospital (UT)
Associated Regional & University Pathologists (UT)
Atlantic Health System (NJ)
Aurora Consolidated Laboratories (WI)
AZ Sint-Jan (Belgium)
Azienda Ospedale Di Lecco (Italy)
Barnes-Jewish Hospital (MO)
Baxter Regional Medical Center (AR)
Baystate Medical Center (MA)
Bbaguas Duzen Laboratories (Turkey)
BC Biomedical Laboratories (Surrey, BC, Canada)
Bermuda Hospitals Board
Boulder Community Hospital (CO)
Brazosport Memorial Hospital (TX)
Broward General Medical Center (FL)
Cadham Provincial Laboratory (Winnipeg, MB, Canada)
Calgary Laboratory Services (Calgary, AB, Canada)
California Pacific Medical Center
Canterbury Health Laboratories (New Zealand)
Cape Breton Healthcare Complex (Nova Scotia, Canada)
Carilion Consolidated Laboratory (VA)
Carolinas Medical Center (NC)
Cathay General Hospital (Taiwan)
Central Texas Veterans Health Care System
Centro Diagnostico Italiano (Milano, Italy)
Champlain Valley Physicians Hospital (NY)
Chang Gung Memorial Hospital (Taiwan)
Changi General Hospital (Singapore)
Children's Hospital (NE)
Children's Hospital & Clinics (MN)
Children's Hospital Medical Center (Akron, OH)
Children's Medical Center of Dallas (TX)
CHR St. Joseph Warquignies (Belgium)
Christus St. John Hospital (TX)
Clarian Health - Methodist Hospital (IN)
CLSI Laboratories (PA)
Community Hospital of Lancaster (PA)
Community Hospital of the Monterey Peninsula (CA)
CompuNet Clinical Laboratories (OH)
Cook Children's Medical Center (TX)
Cook County Hospital (IL)
Covance Central Laboratory Services (IN)
Creighton University Medical Center (NE)
Danish Veterinary Laboratory (Denmark)
Detroit Health Department (MI)
DFS/CLIA Certification (NC)
Diagnósticos da América S/A (Brazil)
Dr. Everett Chalmers Hospital (New Brunswick, Canada)
Duke University Medical Center (NC)
Dwight David Eisenhower Army Medical Center (GA)
Eastern Health Pathology (Australia)
EMH Regional Medical Center (OH)
Emory University Hospital (GA)
Enzo Clinical Labs (NY)
Evangelical Community Hospital (PA)
Fairview-University Medical Center (MN)
Florida Hospital East Orlando
Focus Technologies (CA)
Focus Technologies (VA)
Foothills Hospital (Calgary, AB, Canada)
Franciscan Shared Laboratory (WI)
Fresno Community Hospital and Medical Center
Gamma Dynacare Medical Laboratories (Ontario, Canada)
Geisinger Medical Center (PA)
Guthrie Clinic Laboratories (PA)
Hagerstown Medical Laboratory (MD)
Harris Methodist Fort Worth (TX)
Hartford Hospital (CT)

Headwaters Health Authority (Alberta, Canada)
Health Network Lab (PA)
Health Partners Laboratories (VA)
Highlands Regional Medical Center (FL)
Hoag Memorial Hospital Presbyterian (CA)
Holy Cross Hospital (MD)
Hôpital du Sacré-Coeur de Montreal (Montreal, Quebec, Canada)
Hôpital Maisonneuve - Rosemont (Montreal, Canada)
Hôpital Saint-Luc (Montreal, Quebec, Canada)
Hospital Consolidated Laboratories (MI)
Hospital for Sick Children (Toronto, ON, Canada)
Hospital Sousa Martins (Portugal)
Hotel Dieu Grace Hospital (Windsor, ON, Canada)
Huddinge University Hospital (Sweden)
Hunter Area Health Service (Australia)
Indiana University
Innova Fairfax Hospital (VA)
Institute of Medical and Veterinary Science (Australia)
International Health Management Associates, Inc. (IL)
Jackson Memorial Hospital (FL)
Jacobi Medical Center (NY)
John C. Lincoln Hospital (AZ)
Johns Hopkins Medical Institutions (MD)
Kadlec Medical Center (WA)
Kaiser Permanente (MD)
Kangnam St. Mary's Hospital (Korea)
Kantonsspital (Switzerland)
Kenora-Rainy River Regional Laboratory Program (Ontario, Canada)
Kimball Medical Center (NJ)
King Faisal Specialist Hospital (Saudi Arabia)
LabCorp (NC)
Laboratoire de Santé Publique du Quebec (Canada)
Laboratorio Dr. Echevarne (Spain)
Laboratório Fleury S/C Ltda. (Brazil)
Laboratorio Manlab (Argentina)
Laboratory Corporation of America (NJ)
LAC and USC Healthcare Network (CA)
Lakeland Regional Medical Center (FL)
Landstuhl Regional Medical Center (APO AE)
LeBonheur Children's Medical Center (TN)
Lewis-Gale Medical Center (VA)
L'Hotel-Dieu de Quebec (Canada)
Libero Instituto Univ. Campus BioMedico (Italy)
Loma Linda Mercantile (CA)
Long Beach Memorial Medical Center (CA)
Louisiana State University Medical Center
Lourdes Hospital (KY)
Maccabi Medical Care and Health Fund (Israel)
Magnolia Regional Health Center (MS)
Maimonides Medical Center (NY)
Marion County Health Department (IN)
Martin Luther King/Drew Medical Center (CA)
Massachusetts General Hospital (Microbiology Laboratory)
MDS Metro Laboratory Services (Burnaby, BC, Canada)
Medical College of Virginia Hospital
Memorial Medical Center (Napoleon Avenue, New Orleans, LA)
Memorial Medical Center (Jefferson Davis Pkwy., New Orleans, LA)
Methodist Hospital (TX)
Michigan Department of Community Health
Mid America Clinical Laboratories, LLC (IN)
Middlesex Hospital (CT)
Monmouth Medical Center (NJ)
Montreal Children's Hospital (Canada)
Montreal General Hospital (Canada)
National Serology Reference Laboratory (Australia)
NB Department of Health & Wellness (New Brunswick, Canada)
The Nebraska Medical Center
New Britain General Hospital (CT)
New England Fertility Institute (CT)
New England Medical Center (MA)
New York University Medical Center
NorDx (ME)
North Carolina State Laboratory of Public Health
North Central Medical Center (TX)
North Shore - Long Island Jewish Health System Laboratories (NY)
North Shore University Hospital (NY)
Northwestern Memorial Hospital (IL)
Ochsner Clinic Foundation (LA)
O.L. Vrouwziekenhuis (Belgium)
Ordre professionnel des technologists médicaux du Québec
Orlando Regional Healthcare System (FL)
Ospedali Riuniti (Italy)
The Ottawa Hospital (Ottawa, ON, Canada)
OU Medical Center (OK)
Our Lady of the Resurrection Medical Center (IL)
Pathology and Cytology Laboratories, Inc. (KY)
Pathology Associates Medical Laboratories (WA)
Peking University Shenzhen Hospital (China)
The Permanente Medical Group (CA)
Piedmont Hospital (GA)
Pocono Medical Center (PA)
Providence Health Care (Vancouver, BC, Canada)
Provincial Laboratory for Public Health (Edmonton, AB, Canada)
Queen Elizabeth Hospital (Prince Edward Island, Canada)
Queensland Health Pathology Services (Australia)
Quest Diagnostics Incorporated (CA)
Quintiles Laboratories, Ltd. (GA)
Regions Hospital
Rex Healthcare (NC)
Rhode Island Department of Health Laboratories
Riverside Medical Center (IL)
Robert Wood Johnson University Hospital (NJ)
Royal Columbian Hospital (New Westminster, BC, Canada)
Sahlgrenska Universitetssjukhuset (Sweden)
St. Alexius Medical Center (ND)
St. Anthony Hospital (CO)
St. Anthony's Hospital (FL)
St. Barnabas Medical Center (NJ)
St-Eustache Hospital (Quebec, Canada)
St. Francis Medical Ctr. (CA)
St. John Hospital and Medical Center (MI)
St. John's Hospital & Health Center (CA)
St. Joseph Mercy Hospital (MI)
St. Joseph's Hospital - Marshfield Clinic (WI)
St. Joseph's Hospital & Medical Center (AZ)
St. Jude Children's Research Hospital (TN)
St. Mary of the Plains Hospital (TX)
St. Michael's Hospital (Toronto, ON, Canada)
Ste. Justine Hospital (Montreal, PQ, Canada)
Salem Clinic (OR)
San Francisco General Hospital (CA)
Santa Clara Valley Medical Center (CA)
Seoul Nat'l University Hospital (Korea)
Shands at the University of Florida
South Bend Medical Foundation (IN)
South Western Area Pathology Service (Australia)
Southern Maine Medical Center
Southwest Texas Methodist Hospital
Spartanburg Regional Medical Center (SC)
Specialty Laboratories, Inc. (CA)
State of Connecticut Dept. of Public Health
State of Washington Department of Health
Stony Brook University Hospital (NY)
Stormont-Vail Regional Medical Center (KS)
Sun Health-Boswell Hospital (AZ)
Sunnybrook Health Science Center (ON, Canada)
Swedish Medical Center - Providence Campus (WA)
Temple University Hospital (PA)
Tenet Odessa Regional Hospital (TX)
The Toledo Hospital (OH)
Touro Infirmary (LA)
Tripler Army Medical Center (HI)
Truman Medical Center (MO)
UCLA Medical Center (CA)
UCSF Medical Center (CA)
UNC Hospitals (NC)
Unidad de Patologia Clinica (Mexico)
Union Clinical Laboratory (Taiwan)
Universita Campus Bio-Medico (Italy)
University College Hospital (Galway, Ireland)
University Hospitals of Cleveland (OH)
University of Alabama-Birmingham Hospital
University of Chicago Hospitals (IL)
University of Colorado Hospital
University of Debrecen Medical Health and Science Center (Hungary)
University of Illinois Medical Center
University of the Ryukyus (Japan)
The University of Texas Medical Branch
The University of the West Indies
University of Virginia Medical Center
University of Washington
UZ-KUL Medical Center (Belgium)
VA (Hampton) Medical Center (VA)
VA (Hines) Medical Center (IL)
VA (Tuskegee) Medical Center (AL)
Valley Children's Hospital (CA)
Vejle Hospital (Denmark)
Virginia Beach General Hospital (VA)
Virginia Department of Health
Virginia Regional Medical Center (MN)
ViroMed Laboratories (MN)
Washington Adventist Hospital (MD)
Washoe Medical Center Laboratory (NV)
Waterford Regional Hospital (Ireland)
Wellstar Health Systems (GA)
West Jefferson Medical Center (LA)
Wilford Hall Medical Center (TX)
William Beaumont Army Medical Center (TX)
William Beaumont Hospital (MI)
William Osler Health Centre (Brampton, ON, Canada)
Winn Army Community Hospital (GA)
Winnipeg Regional Health Authority (Winnipeg, Canada)
Wishard Memorial Hospital (IN)
Yonsei University College of Medicine (Korea)
York Hospital (PA)

NCCLS ▼ 940 West Valley Road ▼ Suite 1400 ▼ Wayne, PA 19087 ▼ USA ▼ PHONE 610.688.0100
FAX 610.688.0700 ▼ E-MAIL: exoffice@nccls.org ▼ WEBSITE: www.nccls.org ▼ ISBN 1-56238-540-2