Quality in the Coagulation Laboratory: Trending Standardization and EQA

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• NASCOLA is a nonprofit organization whose mission is to improve diagnostic coagulation testing, through proficiency testing, critical evaluation, guideline development, enhanced communication, collaboration, education, and research

• PT/EQA challenges include normal and abnormal clinical samples distributed as lyophilized sample sets in collaboration with ECAT Foundation

• Contact us at https://www.nascola.com/About/Contact

• Visit our website at www.nascola.com
Reasons for Guidelines

• Provide recommendations to laboratories and staff as tools to optimize test performance and reporting

• Consistency in test performance

• Consistency in result reporting

• Harmonize results between laboratories
Types of Guidelines

- **Recommendations**
  - Suggestions to be followed
  - Based on evidence or tradition

- **Guidelines**
  - Strong suggestions, consensus based on expert opinion
  - Based on evidence or tradition
  - Must document why modifying guidelines

- **Standards**
  - Evidence based, and must be followed
# Sources of Guideline Development

<table>
<thead>
<tr>
<th>Source</th>
<th>Mechanism of Development</th>
<th>Type</th>
<th>Relevance</th>
<th>Geared Toward</th>
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<tr>
<td>BCSH</td>
<td>Expert Group</td>
<td>Guideline</td>
<td>Specialized</td>
<td>UK</td>
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<tr>
<td>CAP</td>
<td>Expert Individuals</td>
<td>Guideline</td>
<td>Sporadic</td>
<td>US</td>
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<td>CLSI</td>
<td>Consensus Panel</td>
<td>Guideline Standards</td>
<td>Routine &amp; Specialized</td>
<td>World</td>
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<tr>
<td>ICSH</td>
<td>Expert Panel</td>
<td>Guideline</td>
<td>Specialized &amp; Routine</td>
<td>World</td>
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<tr>
<td>ISLH</td>
<td>Evidence Based (?)</td>
<td>Guideline</td>
<td>Specialized (?)</td>
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<td>ISO</td>
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<td>WHO</td>
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</table>

Edited from Richard Marlar

2018 CAMLT Annual Meeting Sep 30, 2018
Issues associated with Hemostasis Guidelines

- Too few and too many
  - Too few: less than half of the coagulation testing has relevant guidelines
  - Too many: multiple organizations with guideline on same topic (e.g. lupus anticoagulant testing), without total harmonization
- How long are they valid?
  - Dynamic field that is changing
  - Length of document approvals
- Accessibility
  - No-charge (journals, only if open access)
  - Some must be purchased
- No complete list of guidance documents readily available (ISLH website; NASCOLA considering)
Issues associated with Hemostasis Guidelines

• Clinical and Laboratory Standards Institute
  • Multiple disciplines (e.g. chemistry, microbiology), multiple platforms (standards, guidelines, companion diagnostics), test, methods, administrative and instrumentation evaluation documents
  • Historical resource for hemostasis guidelines
    • Hemostasis guidelines: $140.00 each if non-member
• Changes to CLSI process:
  • Proposed documents no longer decided at the area committee level
  • Maximum number of documents per area committee per year, including revisions, is 3
  • Area committee for Hematology, now includes immunology in addition to hemostasis
  • Decision for proposed guideline heavily dependent upon proposed sales.
  • Takes 1.5 – 2+ years from proposal to publication
CLSI Hemostasis guidelines:

- H47-A2 One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test, 2nd Edition 05/30/2008
- H48-Ed2 Determination of Coagulation Factor Activities Using the One-Stage Clotting Assay, 2nd Edition 03/30/2016
- H54-A Procedures for Validation of INR and Local Calibration of PT/INR Systems, 1st Edition 08/19/2005
- H59-A Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease, 1st Edition 03/31/2011
- H60-A Laboratory Testing for the Lupus Anticoagulant, 1st Edition 04/04/2014
- CLSI H51-A Assays of von Willebrand Factor Antigen and Ristocetin Cofactor Activity 09/01/2002 (Revision prepared, completed, CLSI decision not to publish, not listed)

For purchase – LMIC may be eligible for freebies
British Society for Haematology (BSH)

• Formerly British Committee for Standards in Haematology
• Open access guidelines (aka free)
• Some graded (evidence based)
• Some expert opinion
• Clinical management, diagnosis, or laboratory guidelines
• More recent than CLSI
BSH Hemostasis testing guidelines

- Issued: **01/06/2015** Guideline Diagnosis and Management of Von Willebrand Disease
- Issued: **21/08/2014** Guideline Diagnosis and Management of Rare Coagulation Disorders
- Issued: **06/08/2014** Guideline Measurement of Non-Coumarin Anticoagulants and Their Effects on Tests of Haemostasis
- Issued: **14/06/2014** Guideline Diagnosis and Management of Acquired Coagulation Factor Inhibitor
- Issued: **01/07/2013** Guideline Diagnosis and Treatment of Factor VIII and IX Inhibitors in Congenital Haemophilia
- Issued: **25/05/2012** Guideline Investigation and Management of Antiphospholipid Syndrome
- Issued: **08/02/2012** Guideline Laboratory Investigation of Heritable Disorders of Platelet Function
- Issued: **11/03/2010** Guideline Testing for Heritable Thrombophilia
- Issued: **26/07/2006** Guideline Fibrinogen Assays
# ISTH/SSC Hemostasis testing guidelines

<table>
<thead>
<tr>
<th>SSC Committee</th>
<th>Publication years</th>
<th>Potency standard</th>
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<tr>
<td>Biorheology Subcommittee</td>
<td>2011, 2014</td>
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<tr>
<td>Factor VIII, Factor IX, and Rare Coagulation Disorders Subcommittee</td>
<td>2011 - 2014</td>
<td>2011, 2012</td>
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<tr>
<td>Perinatal and Paediatric Haemostasis Subcommittee</td>
<td>2012</td>
<td></td>
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<tr>
<td>Subcommittee on Control of Anticoagulation</td>
<td>2011, 2012 (x2), 2013 (x2)</td>
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<tr>
<td>Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders</td>
<td>2014</td>
<td>2014</td>
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<tr>
<td>Subcommittee on Factor XI and the Contact System</td>
<td>2011</td>
<td></td>
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<tr>
<td>Subcommittee on Fibrinolysis</td>
<td>2016, 2017</td>
<td></td>
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<tr>
<td>Subcommittee on Haemostasis and Malignancy</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>Subcommittee on Lupus Anticoagulant/Phospholipid/Dependent Antibodies</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>Subcommittee on Platelet Immunology</td>
<td>2012 (x2), 2015, 2016</td>
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<tr>
<td>Subcommittee on Platelet Physiology</td>
<td>2013, 2015</td>
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<td>Subcommittee on Platelet Physiology</td>
<td>2014</td>
<td></td>
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<tr>
<td>Working Group on Coagulation Standards</td>
<td>2011</td>
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Guidelines in Development

- CAP
  - Protein C
  - Protein S
  - Antithrombin
- CLSI
  - Preanalytical variables
  - Heparin Induced Thrombocytopenia
- ICSH
  - Preanalytical variables
  - Direct oral anticoagulants
  - Factor VIII and IX inhibitor assays
  - APTT Mixing studies
  - Coag critical values
  - ADAMTS-13 testing
- NASCOLA
  - Lot-to-lot validation
- ISO
  - Unknown
- ISLH
  - Considering participation
- ISTH-SSC
  - Protein C
  - Protein S
  - Antithrombin
  - Activated Protein C Resistance
- BCSH
  - Unknown
- WHO
  - Unknown
ICSH Guideline:
DOAC Measurements

AIM:
• Intended as laboratory guideline
  • Not intended for, or recommending, whether patients should get tested while on DOACs
• Evidence based (peer-reviewed publications) or expert opinion with consensus
ICSH DOAC Committee members

• Dot Adcock - USA
• Shannon Bates - Canada
• Jonathan Douxfils - Belgium
• Robert Gosselin – USA (Chair)
• Isabelle Gouin-Thibault - France
• Cecilia Guillermo - Uruguay
• Emmanuel Favalaro - Australia
• Steve Kitchen - United Kingdom
• Yohko Kawai - Japan
• Edie Lindhoff-Last – Germany

Over 100 DOAC related peer-reviewed publications by the committee members
ICSH Lab guidance for DOAC measurement

Document Objective

• Intended as laboratory guidance document
  • Address the three phases of DOAC (laboratory) testing:
    • Pre-analytical (sample acquisition)
    • Analytical (testing)
    • Post-analytical (reporting)
  • Open access (free downloads)
  • Not intended to address merits of patient testing
Laboratory studies do not meet recommendations for clinical guidelines (e.g. GRADE), hence the term “guidance” document was adopted.

Recommendations were based on (1) information from peer reviewed publications about laboratory measurement of DOACs, (2) contributing author’s personal experience/expert opinion and (3) good laboratory practice.

Consensus recommendations indicate agreement by all contributing authors.

- Sticky points were sample stability, screening tests, EQA
Industry was supplied document prior to manuscript publication for input/comments

• Pharma: Boehringer Ingelheim, Bristol-Meyers Squibb, Daiichi Sankyo

• IVD: Siemens Healthcare Diagnostics, Instrumentation Laboratory, Grifols, Diagnostica Stago, Sekisui

ICSH DOAC guideline: Sections

Background and DOAC description

• Drug details (indication, dose, bioavailability, etc)
• Anti-factor IIa DOAC (Dabigatran)
• Anti-Factor Xa DOAC (Rivaroxaban, Apixaban, Edoxaban)
  • Acknowledged recent approval of betrixaban but noted lack of data related to laboratory testing.
ICSH Lab guidance for DOAC measurement

General patient recommendations:

• If non-emergent testing is necessary, recommend trough drug level assessment.
• Recommend DOAC levels be reported in ng/mL units.
• Recommend a comment with each reported DOAC result to indicate lack of DOAC ‘therapeutic ranges’, but cite expected trough levels (correlating with dose) for DOAC-treated patients from published studies.
• Usefulness in randomly (emergent) collected samples?
Sample requirements for DOAC measurements

• Plasma prepared from 3.2% sodium citrate can be used for quantitative and qualitative clot-based and chromogenic assays. Liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) can use serum or plasma.
• Citrated whole blood samples should be processed within 4 hours of collection.
• Plasma samples for dabigatran that cannot be tested within 24 hours of collection should be frozen (stability of 14 months or greater if maintained at 20°C or colder) using monitored freezers or dry ice.
• For thrombin time testing (dabigatran), plasma samples are stable for 4 hours at room temperature.
• Plasma samples for anti-FXa DOACs that cannot be tested within 8 hours of collection should be refrigerated (stability of 48 hours) or frozen (stability of 30 days or greater if maintained at 20°C or colder) using monitored freezers or dry ice.
• Data would suggest that at least three freeze–thaw cycles could be performed without significant loss of activity.
Qualitative assays for DOACs

Consensus screening assay recommendations:

• The PT and/or APTT may not be reliable to detect the presence of ‘on-therapy’ concentrations of all DOACs.
• PT and APTT are not responsive to ‘on-therapy’ apixaban levels.
• The PT and APTT should not be used to quantify DOAC concentration.
• In a patient with known DOAC exposure, a prolonged PT or APTT should be considered secondary to drug effect until proven otherwise, and in emergent or life-threatening conditions, tests for quantifying DOAC should be performed to aid in patient management.
Consensus screening assay recommendations, con’t:

• A normal TT excludes the presence of significant dabigatran concentration.
• At the time of writing this article, there is not enough clear data to support the use of TEG or ROTEM for detecting DOAC anticoagulant activity.
• Nonspecific POCT methods may not have sufficient responsiveness to detect DOAC presence.
• Urine DOAC screening tests may provide a rapid assessment (qualitative and semiquantitative) of recent DOAC exposure, but may not reflect circulating drug presence or concentration.
Quantitative Assays for DOAC Measurement

Consensus LC-MS/MS recommendations:

- LC-MS/MS should be considered the gold standard test for measuring DOAC concentration.
- A suitable internal standard for each DOAC is mandatory.
- DOAC metabolites, that are pharmacologically active, should be reported.
Other Methods for Quantifying Anti-FIIa (Dabigatran)

- Demonstrated to be comparable to LC-MS/MS, drug-calibrated DTT, ECA, ECT and anti-FIIa chromogenic methods are recommended as suitable methods to provide rapid quantitation of dabigatran
Other Methods for Quantifying Anti-Xa DOACs

- Demonstrated to be comparable to LC-MS/MS; drug-calibrated anti-FXa is recommended as suitable methods to provide rapid quantitation of anti-Xa DOACs.

- Antithrombin supplemented anti-FXa methods should not be used for DOAC assessment, as these methods tend to overestimate drug concentration and are not validated by the manufacturers.
ICSH Lab guidance for DOAC measurement

POCT and assays in development

• No recommendations, but alerted readership to current (at time of writing) studies.
Quantifying DOACs: Assay Validation or Verification of Performance:

- Method validation or verification of performance is required before assays are used for clinical reporting.
- Prior to performing method validation or verification, a plan (protocol) should be written that describes how the validation will be conducted and acceptance criteria.
- Method validation studies should include precision, accuracy, linearity, determination of LLOQ, LLOD and reportable range and may include stability studies.
- Method verification of performance studies should include precision, accuracy and possibly linearity.
DOAC External Quality Assessment/Assurance

Consensus DOAC EQA recommendations:

• Each laboratory must enroll in an EQA program specific for the DOAC being measured.

• EQA should be at a minimum two samples per dispatch, with at least two dispatches in a calendar year.
ICSH Lab guidance for DOAC measurement

Limitation(s)

Document is fixed, whereas the field is fluidic and changes rapidly

• New drug approvals (betrixaban)
• Minimally addressed impact of secondary drugs on DOAC testing results (e.g. LMWH and anti-Xa DOACs)
• Absence of addressing reversal strategies and impact on DOAC testing (Praxbind, AndexXa)
DOAC measurements using POC

- Dry spot blood collection for mass spec testing Foerster, et al 2018 Anal Chem
- 2018 SSC Dublin
  - Numerous novel POC methods with increased specificity
  - Modification of existing methods
  - Dusting of older methods
ICSH Lab guidance for DOAC measurement

- ICSH proposal - approved
  - Updates to be submitted
    - ~1.5 years (if necessary)
  - Short communication format
    - ~1500 words
- Committee agreed to premise and format
- Planned update for early to mid-2019
ICSH Critical values guidance

Committee members:

Dorothy Adcock, USA
Akbar Dorgalaleh, Iran
Emmanuel Favaloro, Australia
Robert Gosselin, USA (Chair)
Giuseppe Lippi, Italy
Joao Pego, Portugal
Irene Regan, Ireland
Virginie Siguret, France
ICSH Coag Critical Values

- Recent publications on coagulation critical values:
  - Adcock, Lippi, Favaloro
  - Did not provide actual values
- Considering stratifying results
  - Critical – life threatening
  - Emergent – immediate intervention required
  - Warning – action may be required prior to interventions such as epidurals, surgery, etc
- Emphasis on preanalytical criteria met
  - Wrong collection time
  - Wrong test or indication
ICSH Coag Critical Values

Current status:
Committee poll
  Identifying which coagulation test to be considered
  Test with associated value
Poll results:
  Only PT, APTT and FBG were consensus
  High degree variability on values
  Some consideration to patient status
    Acute bleeding
    Operative or Emergency Dept
Next step:
  Defining critical value versus “at risk” values
  Committee member assignments
ICSH Lab guidance documents

Submitting proposals

• Formalized mechanism in progress
• ICSH Administrator
  • Mr Terry Fawcett (admin@icsh.org)
External Quality Assurance

National Committee for Clinical Laboratory Standards (NCCLS, now known as CLSI) introduced the concepts of quality practice for clinical laboratories in 1999.

Goal was to improve all phases of laboratory testing (pre-analytical, analytical and post-analytical processes).

CAP stated benefits: identifying potential test interferences (e.g. medication effect on test results), help to improve laboratories that perform poorly and satisfying regulatory requirements.

Required for all tests performed in the laboratory.
In the United States:
CAP PT is the primary EQA program for satisfying the requirements of CMS accreditation.
CAP EQA (or approved equivalent) is required by CMS for the following routine hemostasis tests:

- Prothrombin time (PT),
- Activated partial thromboplastin time (APTT),
- Fibrinogen (FBG)

For CAP accreditation: following tests must be performed using a CAP approved EQA program:

- International Normalized Ratio (INR),
- D-dimer (XDP),
- Factor VIII activity (F8),
- IgG and IgM anticardiolipin antibodies (ACA),
- Homocysteine (HCY).
Coagulation EQA

For all other hemostasis tests, **EQA can be performed using alternative EQA programs**, even though they may not be approved by CAP or CMS.
# CMS-CAP Approved providers of EQA

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Location</th>
<th>CLIA Approved (PT, APTT, FBG)</th>
<th>CAP Approved (Select analytes)</th>
</tr>
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<tr>
<td>Accutest, Inc</td>
<td>Westford, MA</td>
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<td>College of American Pathologists</td>
<td>Northfield, IL</td>
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<td>Medical Laboratory Evaluation (MLE) Program</td>
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<td>Puerto Rico Proficiency Testing Service</td>
<td>San Juan, PR</td>
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<tr>
<td>Wisconsin State Laboratory of Hygiene</td>
<td>Madison, WI</td>
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</table>
Coagulation EQA: Preanalytical

Common pre-analytical problems associated with coag testing:

- Improper blood collection (wrong tube, wrong patient, wrong collection time, inadequate blood volume in collection tube),
- Processing (incorrect centrifugation, delays processing whole blood),
- Sample condition (lipemia, icterus, hemolysis),
- Storage (room temperature vs refrigerated vs frozen stability).
- Improperly ordered test (PT for assessing unfractionated heparin anticoagulation)
- Inappropriate testing (protein C in a patient receiving warfarin)

None of these are addressed by EQA
Coagulation EQA: Analytical

For the common hemostasis testing, there are adequate samples that provide a good measure for longitudinal and peer-group comparison for test accuracy

PT, APTT and D-dimer

For special coagulation assays the use of contrived samples is more common

Factor assays
Thrombophilia tests
vonWillebrand factor assessment
Coagulation EQA: Analytical

An EQA module could contain a normal sample (usually a commercially prepared normal control or normal pooled plasma) and saline diluted sample of the same material to achieve a reduction in coagulation factors.

However, this material which could identify normal and abnormal factor levels, would not be adequate for assessing other tests that would not be affected by saline dilution (e.g. euglobulin lysis time or positive mixing studies).

In real practice, a saline diluted sample would be cause for rejection.
Most EQA programs do not address the needs of special coagulation laboratories with complex esoteric test menus.

- Factor inhibitor assays,
- HIT assays
- ADAMTS-13 testing.

Some of these esoteric coagulation tests also lack commercial quality control material (e.g. non-factor VIII inhibitor assay, euglobulin lysis time, platelet aggregation studies) that further adds an element of uncertainty to the test accuracy.
EQA programs that do not adequately evaluate the laboratory methods should be assessed using either alternative EQA strategies or internal QA program. This longitudinal evaluation is optimal to assure accurate patient testing for those special coagulation measurands.

Ideally, use of patient derived samples would be more representative of current clinical practice. Avoid using contrived, especially saline diluted or drug contrived samples.
Coagulation EQA: Post-Analytical

- EQA programs can assess the competence of an institution's protocol for manually inputting test results (manual keyboard entry from a computer).

- For some EQA modules and some analytes within a module, there are sections for interpretation, but these are typically limited to either “normal” or “abnormal”.

- Does not reflect clinical practice which would look at all the tests in totality and not just an individual result, in order to provide an interpretation.
Coagulation EQA: Post-Analytical

- Does not address age adjusted reference ranges for reported results, (a low protein C in a neonate would be considered normal whereas in an adult patient would be considered to be significantly low).

- A majority of contrived samples would be rejected outright for testing, and certainly would be addressed as a potential cause of the reported abnormal result.
## Limitations of CAP Coagulation EQA

| Not Available | Factor IX inhibitor  
|---------------| ADAMTS 13 activity  
|               | Apixaban           
|               | TEG/ROTEM parameters |
| Not Abnormal  | Factor XIII  
|               | Euglobulin lysis time  
|               | Factor VIII Inhibitor  
|               | Thromboelastometry  
|               | Non-drug induced platelet abnormalities  
|               | TEG/ROTEM parameters  
|               | Lupus anticoagulant  
|               | Mixing studies (none have true inhibitor) |
| Not Reflect Accuracy for Appropriate Diagnosis | Factor levels associated diagnosis  
|               | (e.g. marked, moderate, or mild hemophilia) |
| Contrived     | Diluted with saline or buffer so all factors are depleted vs. isolated deficiencies  
|               | Diluted with substances that may interfere with (unintended) test performance |
| Does not reflect true patient samples | Lyophilized plasma for Thromboelastography  
|               | Platelet aggregation  
|               | Whole Blood aggregation |
| Abnormalities induced by the same drug | Platelet Aggregation (tirofiban) |
| Does not use institutional reagents | Platelet Aggregation – now entertaining both lab and provided |
North American Specialized Coagulation Laboratory Association (NASCOLA), has partnered with ECAT to provide specialty coagulation EQA for US laboratories.

Modules including:

- Thrombophilia testing,
- ADAMTS-13 testing (normal and abnormal, <20)
- Factor VIII and IX inhibitors (0.5 – 5.0 BU)
- DOACs (Dabi, Riva, Apix).

Forthcoming: modified replacement factors
The NASCOLA/ECAT EQA program:

Uses samples derived from patients

Evaluates post-analytical variables as well,

Larger peer group for assays usually restricted to larger or reference laboratories (e.g. ADAMTS-13, DOACs).

The cost for NASCOLA/ECAT EQA is substantially lower than for certain other programs
The NASCOLA/ECAT EQA program: Post-analytical issues:

One module is based on laboratory testing algorithm and given patient PMH
   Testing is performed at the discretion of the laboratory
   Final diagnosis is graded based on PMH+Labs

Platelet aggregation module:
   Interpretation of provided PRP or WB aggregation graphs
   Clinical history and other relevant laboratory data provided
   Final interpretation is based on graphs+PMH+Labs

Dense granule assessment:
   EMs provided, respondents provide interpretation of images.
Summary

• Laboratory guidance documents are required to assure optimal testing of patient samples

• Currently, there are a number of resources for coagulation related laboratory guidance documents
  CLSI – costs, antiquated
  BSH – open access
  ICSH – open access (N=1)
  SSC/ISTH – access may require membership

• ICSH renewing providing coagulation guidance documents
Summary

• EQA is required for all tests performed in the laboratory

• Satisfying the regulatory requirement does not necessarily assure optimal patient testing

• Enrollment in alternative EQA programs may serve to best identify good and bad laboratory practice, including test performance and post-analytical interpretations