Abbott

Method Evaluation & the *i-STAT PT*^{plus} Cartridge

Best practices for a successful method evaluation of the *i-STAT PT*^{plus} cartridge with the *i-STAT 1* system.

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Method Evaluation of the i-STAT PT^{plus} Cartridge | NPE-5100-REV1-APOC-EN (v1.1) | Revision Date: 27-NOV-2023

INTRODUCTION

In the United States, all laboratory testing is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) law.

OVERSIGHT

CLIA creates federal standards applicable to all U.S. laboratories or sites. This oversight includes method evaluations, which supply objective evidence that a method is fit for purpose, meaning the quality test performance for a specific intended use is fulfilled (CLSI EP15)[1].

It may include the following activities:

- Analytical measurement range: linearity/ calibration verification (CLSI EP6) (12)[2]
- Precision: Measurement of the variability of the new test (CLSI EP5) (11)[3]
- Reference intervals (CLSI EP 28-A3c) (10)[4]
- Trueness/Accuracy: Measurement for comparison to truth (CLSI EP9) (9,10)[5]

TEST COMPLEXITY

Laboratory requirements based on test complexity may be found in the §CLIA 493.[6] To perform moderate complexity testing, a qualified laboratory director provides management and ensures that applicable federal standards are met (§CLIA 493.1405).[6]

The *i-STAT PT*^{plus} cartridge is categorized as a "moderate complexity"[7, 8] test.

Additional activities may be needed for tests categorized as high complexity with responsibilities related to the laboratory's designated technical supervisor (§CLIA 493.1451(b)(4))[6]. Application of standards related to high complexity testing are not applicable to the *i-STAT PT*^{plus} cartridge when used as intended with the *i-STAT 1* system.

METHOD EVALUATION

A method evaluation supplies evidence that the accuracy, precision and reportable range of a new method are adequate to meet the needs of the patient population and clinicians as determined by the laboratory director and/or technical consultant.

The Laboratory Director,

- selects the laboratory staff who will take part in the method evaluation process.
- decides the process and procedures for method evaluation, along with their approval for use.

The method evaluation is not a manufacturer's requirement and specific details, or information related to the above activities may be obtained from your accreditation or regulatory organization.

MANUFACTURER'S QUALITY SYSTEM INSTRUCTIONS

The Manufacturer's Quality System Instructions (MQSI) represent activities necessary to ensure quality results (accuracy, precision, and reliability) based upon the design of the *i-STAT* system.[8]

- Perform Daily Quality Control with Electronic Simulator (Internal, External).
- Check new or replacement analyzers with the Electronic Simulator. (Internal or External).
- Check temperature strip for a new shipment of cartridges or controls.
- Ensure proper cartridge storage.
- Ensure thermal probe check is performed.
- Train staff.
- Update analyzer software.

CONTENTS

The system-based best practices and use recommendations in this document are intended to aid customers with method evaluation activities performed for the *i-STAT PT*^{plus} cartridge using the *i-STAT 1* system.

Analyzers and cartridges should be used by healthcare professionals trained and certified to use the system and should be used according to the facility's policies and procedures.[7]

SUPPORT & SERVICES

With website resources, technical support and implementation services, Abbott provides a number of ways to obtain *i-STAT* product support.

PRODUCT INFORMATION

Visit www.globalpointofcare.abbott to register and access product information. Once logged in, select Support > *i-STAT 1* and *i-STAT Alinity* Support > *i-STAT 1* Resources login. Product information may be found in the following content areas:

- Instructions for Use (IFUs)
- User Guides
- Manuals
- Technical Bulletins

i-STAT LEARNING SYSTEM

Abbott's *i-STAT* learning system provides resources for both the user of the device and the administrator of the point-of-care program.

These resources help support implementation of the product, as well as training and competency activities to meet the testing personnel requirements of your regulatory or accreditation agency when using the *i-STAT* System.

TECHNICAL SUPPORT

Abbott is prepared to assist with any questions regarding our *i-STAT* family of products.

- **For customers in the United States:**
  E-mail: techsvc@abbott.com
- **For customers Outside of the United States:**
  E-mail: oustechsvc@abbott.com

ADDITIONAL SERVICES

Abbott provides customers with additional options for services, such as implementation support and statistical analysis. Customers may work with their Abbott representative for availability of service solutions pertaining to:

- Support of various activities that are part of a successful implementation.
- Statistical analysis using data requirements provided by Abbott.

PRODUCTS

i-STAT PT^{plus} CARTRIDGE (REF/LIST NUMBER 03P89-50)

The *i-STAT PT*^{plus} cartridge is intended for use in the *in vitro* quantitative measurement of the clot time of the extrinsic coagulation pathway when activated by thromboplastin in non-anticoagulated whole blood (venous or capillary), using the *i-STAT 1* system.[7]

Measurements of prothrombin time are used to aid in the monitoring of patients receiving anticoagulant therapy with coumarin derivatives.[7]

The *i-STAT PT*^{plus} Prothrombin Time test result is reported in seconds and as an International Normalized Ratio (INR).[7] The test is intended for point of care use and is for prescription use only.[7]

i-STAT 1 SYSTEM

The *i-STAT 1* System incorporates a comprehensive group of components needed to perform blood analysis at the point of care.[8] An analyzer, a cartridge with the required tests, and 2-3 drops of blood will allow the caregiver to view quantitative test results.[8]

The *i-STAT 1* analyzer and i-*STAT 1 Wireless* analyzer are intended for use in the *in vitro* quantification of various analytes in whole blood or plasma in point of care or clinical laboratory settings.[8] The *i-STAT 1* analyzer is used in conjunction with *i-STAT* cartridges for the simultaneous quantitative determination of specific analytes in whole blood.[8]

LIQUID QUALITY CONTROL MATERIALS

Liquid quality controls are used to verify the integrity of newly received cartridges and their storage conditions.[8]

The *i-STAT PT*^{plus} controls, Level 1 and Level 2, are intended for use with the *i-STAT PT*^{plus} cartridge (REF 03P89-50) on the *i-STAT 1* system.[7]

i-STAT PT^{plus} CONTROL LEVEL 1 (REF/LIST NUMBER 06P17-17)

The *i-STAT PT*^{plus} control level 1 has been formulated to produce a normal/non-therapeutic prothrombin time and is designed to provide results within a range of 0.8–1.6 INR.[7]

i-STAT PT^{plus} CONTROL LEVEL 2 (REF/LIST NUMBER 06P17-18)

The *i-STAT PT*^{plus} control level 2 has been formulated to produce a therapeutic prothrombin time and is designed to provide results within a range of 1.7–3.5 INR.[7]

VALUE ASSIGNMENT SHEETS (VAS)

Value Assignment Sheets provide the acceptable range for each level of control materials based on cartridge lot and control lot numbers. Value Assignment Sheets are available on the Support page of Abbott's website; visit www.globalpointofcare.abbott. Ensure that you maintain the Value Assignment Sheets used during the method evaluation with your records.

PREPARATION

Prior to performing a method evaluation, Abbott recommends review of the cartridge and liquid quality control material Instructions for Use (IFU) and device user guides and system manuals.

Visit www.globalpointofcare.abbott to register and access product information. Once logged in, select Support > *i-STAT 1* and *i-STAT* Alinity Support > *i-STAT 1* Resources login.

LABORATORY PERSONNEL

The laboratory director must ensure that the staff selected are healthcare professionals trained and competent to use the system, along with any related facility policies and procedures.

EQUIPMENT

Every *i-STAT* device used with the *i-STAT PT*^{plus} cartridge for patient testing may be included in the method evaluation.

For laboratories following CLIA regulations or Accrediting Organization's standards, each instrument's performance must be verified – even if there are multiple instruments of the same make and model (§CLIA 493.1253(b)(1)).[9]

Per CAP's COM.40000 Method Validation and Verification Approval - Nonwaived Tests Phase II, if multiple identical instruments or devices are in use, there must be records showing that the method performance specifications have been separately verified for each test and instrument or device.[10]

As the interpretation of regulations and standards provided by accreditation organizations varies, the Laboratory director identifies and implements their laboratory accreditor's requirements.

NOTE: Services available from Abbott for implementation and statistical analysis require at least two *i-STAT 1* devices for duplicate testing to supply the imprecision data required by statistical analysis software.

SOFTWARE REQUIREMENTS

The following software requirements are required prior to starting the method evaluation:

- *i-STAT 1* analyzer software version – CLEW A47/ JAMS156 or higher.
- i-STAT/DE - Version 2.11 with patch for *i-STAT PT*^{plus} cartridge or higher.

ANALYZER CONFIGURATION OR CUSTOMIZATION

For best results, ensure that all *i-STAT 1* devices are configured with the correct date, time and software version.

- Refer to the *i-STAT 1* User Guide or System Manual for customization via the analyzer keypad.
- If using i-STAT/DE to customize the analyzer, refer to the Customization Workspace section of the i-STAT/DE User Guide.

CONSUMABLES

USING THE CONSUMABLE CALCULATION WORKSHEET

Customers should ensure that they have enough products to perform the activities for method evaluation as defined by their laboratory director.

To aid customers with ordering i-STAT consumables (i.e., cartridges, liquid quality control, etc) for the method evaluation, a worksheet is provided on the next page. The worksheet may be used to calculate the number of i-STAT consumables required by entering the number of tests performed in each activity multiplied by the number of devices included in the study.

Implementation service options available from Abbott for statistical analysis require use of this worksheet to ensure that requirements are met for the final statistical report.

STUDY	CALCULATION	TOTAL (Example)
PRECISION • Minimum of 20 replicates for each level over two days, includes all devices. • Each box of controls provides 5 liquid control samples for testing. • Additional cartridges may be tested with the remaining fluid, if used within 30 seconds of complete reconstitution of the sample.	Control Level 1 x # of devices	N = • 20 cartridges or 1 box of cartridges (minimum) • 4 boxes of level 1 (maximum)
	Control Level 2 x # of devices	N = • 20 cartridges or 1 box of cartridges (minimum) • 4 boxes of level 2 (maximum)
METHOD COMPARISON (ACCURACY) • Includes all devices.	Number of Samples x 2 (for duplicates) x # of devices	For example - two analyzers and 20 samples, N = • 40 cartridges or 2 boxes of cartridges
MEAN NORMAL PT (MNPT) (OPTIONAL) • 20 normal donors; can include samples from method comparison. • Include all devices. The samples are tested in singlet as this study is not being performed for statistical analysis. • When using normal INR results from the method comparison study data, the first result from each instrument may be used.	At least 20 INR results from normal donors not on oral anticoagulant (OAT).	N = • 20 cartridges or 1 box of cartridges (minimum)
PERFORMANCE VERIFICATION (REPORTABLE RANGE) • At least three samples representing low, mid and high values within the reportable range. Include all devices.	Number of devices x 3 cartridges	For example - two analyzers, N = • 6 cartridges (minimum)
REFERENCE INTERVALS: Results from the method comparison for accuracy and performance verification of the reportable range may be used to verify the reference intervals.		

i-STAT PT^{PLUS} CARTRIDGE CONSUMABLE CALCULATION WORKSHEET

ORDERING INFORMATION

CONSUMABLE NAME	PRODUCT REF/LIST NUMBER	QUANTITY PER BOX
i-STAT PT^{plus} **Cartridge**	**03P89-50**	**25**
i-STAT PT^{plus} ***Control*** **Level 1**	**06P17-17**	**5 tests (minimum)***
i-STAT PT^{plus} ***Control*** **Level 2**	**06P17-18**	**5 tests (minimum)***

* **For controls, additonal *i-STAT PT*^{plus} cartridges may be tested with the remaining fluid if tested used within 30 seconds of complete reconstitution of the sample.**

CONSUMABLE CALCULATION WORKSHEET

STUDY	CALCULATION	TOTAL
PRECISION	Control Level 1 x # of devices	
	Control Level 2 x # of devices	
METHOD COMPARISON (ACCURACY)	Number of Samples x 2 (for duplicates) x # of devices	
MEAN NORMAL PT (MNPT) (OPTIONAL)	At least 20 INR results from normal donors not on oral anticoagulant (OAT); can include samples from method comparison. .	
PERFORMANCE VERIFICATION (REPORTABLE RANGE)	Number of devices x 3 cartridges	
REFERENCE INTERVALS: Results from the method comparison and performance verification studies may be used to verify the reference intervals.		

METHOD COMPARISON

Accuracy is verified by comparing results to a definitive or reference method, or an established comparative method.[11] Laboratory practice may require testing for accuracy which is typically accomplished by a method comparison study. Use of matrix-appropriate reference materials, patient specimens (altered or unaltered), or other commutable materials with known concentration or activities may be used to verify accuracy.[11]

If a method comparison (accuracy) study is performed, it is preferable to compare to the core/main laboratory method. The comparative instrument method's make, model, reagent lot number, ISI and mean normal PT time should be recorded.

TESTING CONSIDERATIONS

To ensure best results, refer to the *i-STAT PT*^{plus} cartridge IFU and the *i-STAT 1* System Manual for pre-requisites, blood collection options and test precautions or limitations prior to performing cartridge testing with the analyzer.

When performing the method comparison consider the following:

DO

- **DO** obtain samples within the clinically relevant range as determined by the laboratory director.
- **DO** use one lot number of cartridges in the method comparison and ensure that cartridges and analyzers used are at room temperature.
- **DO** follow instructions for use for storage and handling of the cartridges, materials or samples.

DO NOT

- **DO NOT** improperly store or handle cartridges. Improper handling and storage may result in quality check codes or unexpected test results.
- **DO NOT** inappropriately use quality controls for accuracy. Depending on the laboratory's accreditor, "quality controls are not considered appropriate materials to use for the method comparison study."[11]

COMPARATIVE METHOD CONSIDERATIONS

Ensure the comparative method uses the World Health Organization (WHO) calculation for INR.

Each manufacturer establishes their own International Sensitivity Index (ISI) and Mean Normal PT time (MNPT).[12]

When no comparative method is available, the laboratory director has the discretion to use available regulatory compliance guidance for verifying accuracy.

For example, the CLIA guidance, *Verification of Performance Verifications*[13], states that "the laboratory needs to compare the accuracy of the test results it obtains when using a test system with the manufacturer's accuracy claims."[13]

Per the CLIA guidance, the laboratory can test "commercially available calibrators/calibration or quality control (QC) materials with known values, proficiency testing materials that have established values, or previously tested patient specimens with established values." [13]

Also per the CLIA guidance, the laboratory can compare "results of tests performed by the laboratory against the results of a reference method, or comparing split sample results with results obtained from another method which have already been shown to provide accurate results."[13] CAP does not consider quality control materials as appropriate for use in the method comparison study.[11]

COMPARATIVE METHOD CONSIDERATIONS - cont'd

ISI AND MNPT

The traceability of the prothrombin time test in the *i-STAT PT*^{plus} cartridge has been established against the World Health Organization (WHO) International Reference Preparation (IRP) of human recombinant tissue factor (RTF) using the tilt tube technique.[7]

- The *i-STAT PT*^{plus} cartridge is traceable to rTF/16.[7]
- The *i-STAT PT*^{plus} thromboplastin is specific for the i-STAT instrument.[7]
- Calibration and ISI assignment is performed using multiple *i-STAT* devices running *i-STAT* cartridges containing the *i-STAT PT*^{plus} thromboplastin resulting in a factory calibrated PT test.[7]

Mean Normal *i-STAT* prothrombin time (sec) and an International Sensitivity Index (ISI) value are determined following the World Health Organization (WHO) recommendations at a CAP-accredited facility using the available WHO human recombinant thromboplastin reagent.[7]

INR = [Patient *i-STAT* prothrombin time (sec)] X ISI
[Mean Normal *i-STAT* prothrombin time (sec)]

For the *i-STAT PT*^{plus} cartridge, the reported time is derived from the INR result and the equation above using an ISI of 1.0 and a typical mean normal plasma PT time of 10.1 seconds.[7]

REFERNCE INTERVAL (RI) CONSIDERATIONS

To verify the refernce interval using data from the "method comparison study, samples must be collected with an appropriate distribution of values spanning the RI, as an insufficient range may underestimate and a range too large may overestimate the strength of the correlation.unexpected biases or discrepancies in results.[25]

OFF-SITE LABORATORY CONSIDERATIONS

When considering use of an off-site laboratory the following information may be assessed to decide if this approach will yield expected results:

- Samples must be processed exactly as instructed by the off-site laboratory.
- Samples for the off-site laboratory and the *i-STAT* System must be collected at the same time.

Differences in samples and delays in testing caused by transport to the off-site laboratory may cause unexpected biases or discrepancies in results.

CONSIDERATIONS RELATED TO MANUFACTURER ASSISTANCE

Regarding assistance from the manufacturer, the Laboratory Director must verify the standards or regulations from their laboratory accreditor before obtaining the implementation and statistical analysis service options available from Abbott. Laboratory accreditor may or may not allow full or partial assistance from the manufacturer.

For example, the College of American Pathologist (CAP) checklist, COM.40300 "Verification of Test Performance Specifications—FDA-Cleared/ Approved Tests"[11], discusses conditions for when a manufacturer aids a laboratory in setting up a new FDA-approved or -cleared test. It says that "the lab must make sure that the personnel who will perform the test participate in the verification or validation study"[14] and "if the personnel don't participate, there must be some way to confirm that performance is consistent with in-house studies performed by lab personnel."[14]

While COLA says that the manufacturer can "assist by providing materials, procedures and statistical analysis"[15]; the manufacturer "may not perform the actual testing of samples used in the verification process..."[15]

PATIENT SAMPLE CONSIDERATIONS

For statistical analysis, test the determined number of samples in duplicate on the *i-STAT* device(s) that will be used for patient testing with the *i-STAT PT*^{plus} cartridge. Patient samples should also be tested in duplicate on the comparative method.

- The number of samples should be determined by the laboratory director.
- The laboratory director also has discretion on the collection type of the patient samples. This means that they may decide to include both direct finger-stick collection samples and samples collected venously.

The *i-STAT PT*^{plus} does not allow for edits to the ISI or MNPT; it is good laboratory practice to include samples from healthy volunteers who are not on oral anticoagulation therapy (OAT) and not suspected of having coagulopathies in the method comparison. Inclusion of these normal samples can also help verify the low end of the reportable range and show bias that comes from the assigned values in the algorithm that comes from the manufacturer.

NOTE: When using the implementation service option from Abbott for statistical analysis, a minimum of at least 20 patient samples must be tested in duplicate.

ESTABLISHING TARGET INR VALUES FOR PATIENT SAMPLES

The International Normalized Ratio (INR)[16], from the website www.ncbi.nlm.nih.gov states that normal patients who are not on anticoagulation usually have an INR of 1.0, regardless of the ISI of the particular performing laboratory and patients on anticoagulant therapy have a therapeutic INR range between 2.0 to 3.0.

The laboratory director has discretion on defining the target INR values for patient samples, based on the laboratory accreditor'S' standards or CLSI regulations.

EXAMPLES OF TARGET INR VALUES FOR PATIENT SAMPLES

The following are examples of the categorization of INR values:

- In Abbott's studies for the *i-STAT PT*^{plus} cartridge, the following categorization and INR values were used: "non-therapeutic (INR 0.8 – 1.9), therapeutic (INR 2.0 - 4.5), and very high therapeutic (INR 4.6 - 8.0)"[7].
- CLSI states that whole-blood specimens should be tested in the normal range, in the therapeutic range (2.0 to 3.5 INR) and in the supratherapeutic range (> 3.5 INR).[17]
- The table below is an example of patient sample INR target times and the number of patients for each based on a method comparison study requiring 30 samples.
- This example is not being provided as a manufacturers' requirement. The Laboratory Director is responsible for determining the number of samples and the distribution of those samples for target INR ranges.

Target INR Value*	Minimum # of Patients	Estimated Target Plasma PT (sec)
<1.3	5	12.0 – 17.9
1.4 – 2.5	10	18.0 – 26.9
2.6 – 4.0	12	27.0 – 36.9
> 4.0	3	>/= 37.0

*See CLSI guideline *POCT14, Section 4.1.2: Specific Considerations for Point of Care Prothrombin Time/INR Precision.*[17]

METHOD COMPARISON CONTINUED

SAMPLE COLLECTION

The *i-STAT PT*^{plus} cartridge requires fresh whole blood (approximately 20 µL) from venous or capillary samples.[7] Refer to the *i-STAT PT*^{plus} IFU for information on blood collection options and test limitations and interferences. Specimens should be collected according to the facility's policies and procedures.

Laboratories may refer to the following CLSI standards for proper sample collection procedures:

- GP41 - *Collection of Diagnostic Venous Blood Specimens* provides procedures for diagnostic venous blood collection.[19]
- GP42 – *Collection of Capillary Blood Specimens* provides procedures for capillary blood collection, including the specifications for collection sites and puncture depth.[20]
- H21-A5 - *Collection, Transport and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays* provides procedures for plasma-based coagulation testing.[21]

The following should be recorded for each patient included in the method comparison study. This information may be helpful in determining the cause of discrepant results:

- Patient receiving unfractionated or low molecular weight heparin.
- Difficulty collecting sample (fingerstick or venipuncture) .
- Under-filled sodium citrate evacuated tube.

CAPILLARY SAMPLES

The skin-puncture and the *i-STAT PT*^{plus} cartridge test should be performed either immediately before or after the venipuncture collection of the sodium citrate, when using plasma for the comparative method.

When performing duplicate testing, two cartridges should be filled from the same finger puncture, when possible. If a second skin puncture is required, ensure that the additional collection information is recorded with the result.

LANCETS

As single-use lancets vary with depths of 1.5 to 3.0 mm, selection of the lancet should be based on the facility's policies and procedures for collecting capillary samples. For example, when collecting a capillary sample from adults using "a finger-prick, the depth should not go beyond 2.4 mm, so a 2.2 mm lancet is the longest length typically used."[12]

The facility's policies and procedures may also provide recommended lancet depths for neonates and pediatrics. For example "in heel-pricks, the depth should not go beyond 2.4 mm" and "a 0.85 mm lancet is available" for premature neonates.[12]

CAPILLARY SAMPLE CONSIDERATIONS

When collecting capillary samples, consider the following:

DO

- **DO** use a collection technique resulting in good blood flow. Inadequate blood flow may produce erroneous results.
- **DO** allow the collection site to dry thoroughly before sampling. Allowing residual alcohol to dry over the collection site helps avoid hemolysis of sample.
- **DO** fill the cartridge directly from the skin-puncture site.
- **DO** immediately apply the sample to the sample well of the cartridge. If a second measurement is required, a fresh sample should be obtained.

CAPILLARY SAMPLE TESTING CONSIDERATIONS - cont'd

DO NOT

- **DO NOT** disinfect capillary puncture site with swabs or solutions containing substances other than isopropanol. Chlorhexidine digluconate is not recommended. [8]
- **DO NOT** vigorously massage or "milk" the capillary collection site. Avoiding vigorous massage or "milking" of the capillary puncture site helps to prevent hemolysis of the sample.
- **DO NOT** wipe away the first drop of blood.
- **DO NOT** use a capillary tube to transfer the sample from the skin puncture site to the cartridge.

VENOUS SAMPLES

Follow the facility's policy or procedure for the collection of venous samples. For a comparative method using plasma, follow the tube manufacturer's instructions. The sample may also be collected into a plastic evacuated tube without anticoagulant or additives.

For best results, the tube for the comparative method should be centrifuged within 20 minutes of being drawn and tested within 2 hours.

DISCARD TUBES

"When using a winged blood collection set for venipuncture and a coagulation tube is first drawn, draw a discard tube first."[21] Ensure to follow your facility's policy and procedure with regards to the collection of a discard tube. Refer to the instructions provided by the collection device manufacturer for additional recommendations.

VENOUS SAMPLE CONSIDERATIONS

When collecting venous samples, consider the following:

DO

- **DO** use a collection technique resulting in good blood flow. Inadequate blood flow may produce erroneous results.
- **DO** collect a specimen, ensuring proper order of draw, and then fill a 3.2% sodium citrate tube. (Use of a 3.8% sodium citrate tube may contribute to method differences).
- **DO** use a plastic collection device (either a plastic syringe or a plastic evacuated tube). Use of the collection device containing clot activators or serum separator may produce erroneous results.
- **DO** fill the cartridge to the fill line immediately. Delay in filling the cartridge may produce erroneous results. Quality check codes may occur when the sample does not fill reach the cartridge fill line.

DO NOT

- **DO NOT** underfill a sodium citrate tube. Follow tube manufacturer instructions for proper fill level.
- **DO NOT** incorrectly handle or incorrectly fill the cartridge as this may generate quality check codes.
- **DO NOT** use a glass collection device as this may produce erroneous results.
- **DO NOT** use a collection device containing clot activators or serum separator as this may produce erroneous results.

METHOD COMPARISON CONTINUED

ACCEPTABILITY OF METHOD COMPARISON STUDY

The criteria for acceptability of results varies by regulatory agency and publication. The Laboratory Director has discretion on defining the criteria and the acceptability of the results of the study.

According to Reliability of Point of Care International-Normalized-Ratio-Measurements[23]: "A 2016 Food and Drug Administration workshop on POC INR meters recommended 95% of POC INR samples should read within 20% of the reference laboratory method for INRs up to 4.5, but the Food and Drug Administration has not formally adopted this device standard."[23] The International Normalized Ratio (INR)[16], from the website www.ncbi.nlm.nih.gov states that the "INR value from POCT is considered acceptable if it does not exceed plus or minus 0.5 INR units by the reference laboratory INR value."[16] CLSI's POCT14 also provides guidance with regards to acceptability based on INR target values.[17]

The INR calculation may have variability due to differences in the assigned values used by manufacturers. For that reason, the *i-STAT PT*^{plus} cartridge may produce a different result when compared to another method. Although differences should not be clinically significant, the expectation should be that the results will not be a 1:1 match.

"Laboratory professionals should be aware of the potential for POC INR and clinical laboratory INR disagreement and work to develop institutional procedures for confirmatory testing."[23]

RECORDS AND RETENTION

Once the method comparison study has been completed, it is the responsibility of the Laboratory Director to review, approve and store all records associated with the study. These records are part of the evidence to support completion of the method evaluation activities. The laboratory accreditor may have additional guidelines pertaining to the length of time the records are required to be stored.

MEAN NORMAL PT AND INR ASSESSMENT

Performing a mean normal PT (MNPT) and INR study is not a manufacturer's instruction or requirement. When using a Laboratory instrument as a method comparator, the Laboratory Director determines whether to perform a MNPT study based on their accreditor requirements or as a result of reviewing the results from the method comparison study. An optional worksheet for data collection is provided at the end of this section.

For laboratory instruments, the INR is calculated using the patient's PT result (sec), the Mean Normal Plasma Prothrombin Time (MNPT), and a factor called the International Sensitivity Index (ISI). The MNPT and ISI are specific for each lot of Prothrombin reagent used by the laboratory instrument, and these values are updated whenever the lot number changes. If they are not updated correctly, patient results may be impacted, which could lead to a poor method comparison when conducting a performance verification.

To troubleshoot such a situation, a Mean Normal PT Study may be conducted as part of the performance verification. Twenty INR results from normal donors may be collected or selected from the data in the studies for method comparison and/or performance verification across the reportable range from the *i-STAT* analyzer and comparative instrument. More samples may be collected when existing study data does not include 20 INR results from normal donors.

The INR results should be close to 1.0. If the results from the comparative instrument are not close to 1.0, it may indicate that the ISI and/or MNPT are incorrect for that instrument. Troubleshooting the comparative instrument should be done with the help of that instrument manufacturer's technical support team.

METHOD COMPARISON DATA COLLECTION

To aid customers with documenting results for the method comparison study, an optional cover page and worksheet are provided at the end of this section.

DATA COLLECTION

The Laboratory Director defines the process and procedures used to perform the method comparison activities. Based upon those requirements, data related to those activities may be collected. The worksheet provided by Abbott is an optional aid and does not replace data collection instructions from the facility's procedures.

DEVICE & CONSUMABLE INFORMATION

At minium, the model and serial numbers for the devices involved in the method evaluation should be documented. The i-STAT System requires a software update every 6 months. It is important to document the software version of the analyzers at the time that the activities are performed for the method comparison. For best results, Abbott recommends the use of one lot number of *i-STAT* cartridges in the method comparison study. The cartridge lot number details should be captured with the data collection.

If applicable, obtain the following information for the laboratory instrument used as the method comparator:

- Reagent lot numbers
- Reagent calibration date and the lot's ISI and MNPT values

PATIENT HEALTH INFORMATION

"It is incumbent on all covered entities and their business associates to thoroughly comprehend and apply the HIPAA Privacy Rule requirements, ensuring the protection of health information, and thus, fulfilling their roles as guardians of their patients' sensitive data."[22] Follow your facility's policy and procedures for handling patient health information and properly de-identifying when applicable.

Ensure to document the ID number used for the patient samples tested as part of the method comparison. Documenting other considerations related to collection of the sample and medications may assist with troubleshooting of results or when reviewing data in statistical analysis reports.

SAMPLE COLLECTION DATE & TIME

Documenting the collection date and time of the samples provides evidence of meeting procedural test timing requirements. This information may also aid in troubleshooting results.

DATA COLLECTION WORKSHEET

The cover page and worksheet provided may be used by customers in their study or as a guide to create their own. Below is an example of an entry; information displayed in red has been created as part of the example.

EXAMPLE: Using the worksheet to document information and results for a patient sample.

No.	Patient ID#	i-STAT			Enter name of method comparator			Medications & Other Considerations
		Collection Date & Time	PT, INR Values PT , INR 336832	PT , INR 336833	Date & Time Tested on Comparator	PT, INR Values PT , INR	PT, INR	
1	1111	11/27/2023 13:11 PM	18.1 , 1.4	18.3 , 1.4	11/27/2023 13:30 PM	17, 1.3	17, 1.3	10 mg daily, coumadin

i-STAT PT^{plus} CARTRIDGE
METHOD EVALUATION DATA COLLECTION

(COVER PAGE)

FACILITY INFORMATION	
Facility Name & Address:	
Location/Department Name (If applicable):	
Facility Contact(s): (Full Name, E-mail Address, & Phone Number)	**Primary Contact:**
	Additional Contact, if applicable:

METHOD COMPARATOR DETAILS	
Instrument Name:	
Serial Number:	
Reagent Name:	
Reagent Lot Number/ Expiration Date:	
Calibration Date:	
Reagent ISI & MNPT:	

Off-Site Laboratory Name & Address (if applicable)

ADDITIONAL INFORMATION:

TOTAL NUMBER OF PAGES:

METHOD COMPARISON DATA COLLECTION WORKSHEET

REVIEWED BY (PRINT NAME): _____

SIGNATURE AND DATE: _____

i-STAT PT^{plus} CARTRIDGE	
Lot Number:	
Expiration Date:	

i-STAT 1	S/N #	SOFTWARE (CLEW)
Analyzer 1:		
Analyzer 2:		

METHOD COMPARATOR:		
REAGENT	ISI	MNPT

No.	Patient ID#	i-STAT						Medications & Other Considerations
		Collection Date & Time	PT, INR Values PT , INR	PT , INR	Date & Time Tested on Comparator	PT, INR Values PT (INR)	PT (INR)	

PAGE : _____ OF _____

METHOD COMPARISON STUDY
PATIENT TEST QUICK REFERENCE

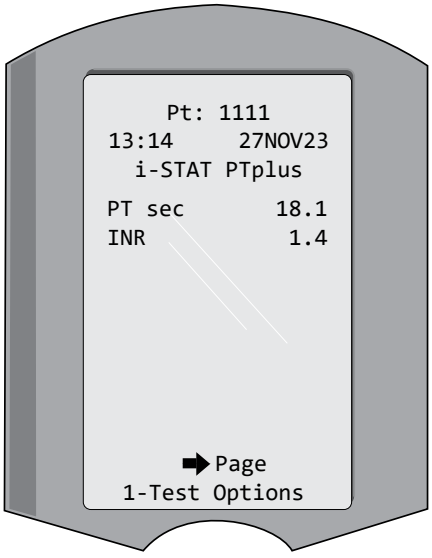
i-STAT 1 ANALYZER & *i-STAT PT^{plus}* CARTRIDGE

ANALYZER PATIENT TEST PROCEDURE OVERVIEW

The following is on overview of the testing procedure and not intended as training. Prior to performing the method comparison study, the Laboratory Director is responsible for ensuring that personnel have been trained to the *i-STAT* System. For testing details, refer to the *i-STAT PT^{plus}* cartridge IFU.

To perform a patient test with the *i-STAT 1* analyzer:

1. Press the power button to turn on the analyzer.
2. Press 2 (i-STAT Cartridge).
3. Follow the analyzer prompts.
4. Scan the lot number on the cartridge pouch barcode.
5. Continue normal procedures for preparing the sample and filling and sealing the cartridge.
6. Push the sealed cartridge into the analyzer's cartridge port until it clicks into place. Wait for the test to complete.
7. Review results. Image below provides an example of a patient test result displayed by the analyzer.



CARTRIDGE HANDLING AND FILLING REMINDERS

CARTRIDGE HANDLING

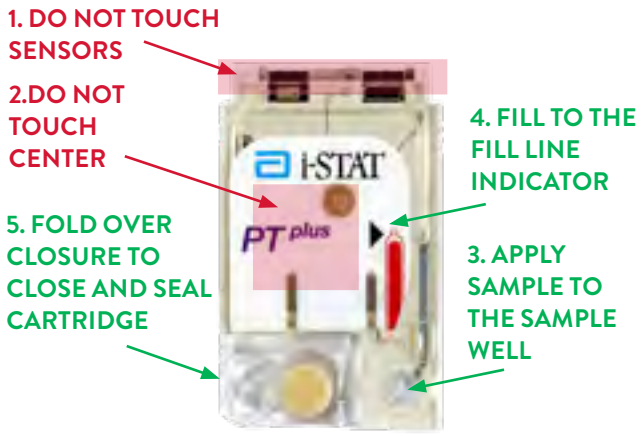
Cartridges and analyzers must be at room temperature prior to testing to prevent environmental quality check codes.

- Cartridge pouch - 5 minutes
- Cartridge Box - 1 hour
- Analyzer - 30 minutes

To prevent quality check codes related to mishandling of the cartridge, ensure that the sensors and center area of the cartridge are not touched. Cartridges should also be placed on a level, clean, non-fibrous surface, free of debris.

FILLING THE CARTRIDGE

To prevent quality check codes related to incorrect filling of the cartridge, fill the cartridge to the fill line indicator. Once filled, ensure that the cartridge is sealed.



MNPT ASSESMENT (OPTIONAL) DATA COLLECTION WORKSHEET

REVIEWED BY (PRINT NAME): _____

SIGNATURE AND DATE: _____

i-STAT PT^{plus} CARTRIDGE	
Lot Number:	
Expiration Date:	

i-STAT 1	S/N #	SOFTWARE (CLEW)
Analyzer 1:		
Analyzer 2:		

METHOD COMPARATOR:		
REAGENT	ISI	MNPT

No.	Patient ID#	i-STAT						Medications & Other Considerations
		Collection Date & Time	PT, INR Values PT , INR	PT , INR	Date & Time Tested on Comparator	PT, INR Values PT (INR)	PT (INR)	

PAGE : _____ OF _____

VERIFICATION OF REFERENCE INTERVALS

Regulatory standards may require the verification of the reference intervals or reference range for the test method.

REFERENCE INTERVALS

Reference intervals (RIs) are fundamental tools used by healthcare and laboratory professionals to interpret patient laboratory test results, ideally enabling differentiation of healthy and unhealthy individuals.[25]

The reference values for INR take into account in PT measurement in device related variations, type of reagents used, and sensitivity differences in the Tissue Factor (TF) activator.[4]

The *i-STAT PT*^{plus} cartridge reference intervals for venous and capillary specimens combined is INR: 0.9–1.3.[7] See the *i-STAT PT*^{plus} IFU for more details.

VERIFYING REFERENCE INTERVALS

The standard approach to verify RIs recommended by the Clinical Laboratory Standards Institute (CLSI) EP28-A3c guideline for routine clinical laboratories is to collect and analyze a minimum of 20 samples from healthy subjects from the local population.[24] Results for health patient samples from the method comparison study may be used towards satisfying the recommendation.

Refer to CLSI EP28-A3c – *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory*; Approved Guideline for information about the use of method comparison data to verify reference range, found at www.clsi.org.

REPORTING REFERENCE INTERVALS

Reference intervals (RIs) are most commonly defined as the central 95% of laboratory test results expected in a healthy reference population.[25]

The Laboratory Director and/or the Technical Consultant/Technical Supervisor need to determine how the laboratory will report results that are greater than the highest verified level or less than the lowest verified level.[14]

PERFORMANCE VERIFICATION OF THE REPORTABLE RANGE

Regulatory standards may require performance verification across the reportable range.[2] Reportable range verification may be met by using matrix appropriate materials, which include low, mid, and high concentrations with recovery of results that fall within a defined range of target values.

REPORTABLE RANGE

The reportable range for the prothrombin time test in the *i-STAT PT*^{plus} cartridge used with the *i-STAT 1* System is 0.8–8.0 INR and 8.1–80.8 seconds.[7]

The *i-STAT PT*^{plus} is a factory calibrated PT test.[7] Calibration verification material is not available since PT and INR tests are a measure of time.

i-STAT PT^{plus} *Controls* do not span the reportable range. Proficiency samples may be acquired from your proficiency provider; which may include samples that span the reportable range.

PERFORMANCE VERIFCATION CONSIDERATIONS

Performance verification of values outside of the therapeutic range and on the lower/higher end of the device's reportable range may not be possible given the lack of commercially available materials or samples that span the full reportable range.

It is the responsibility of the Laboratory Director to:

- determine the samples used for the verification, and the closeness of sample concentrations.
- define the criteria for accepting or rejecting verification of the reportable range.

In the absence of any suitable commercially available control/calibration verification material, patient samples with known values, proficiency testing samples with known results, or reference samples can be used to expand the verified range.

As there are no calibration verificaiton materials available for the *i-STAT PT*^{plus} cartridge, Abbott recommends testing samples using the Patient test option in the analyzer. Results may be documented in the method comparision data collection sheet.

TESTING CONSIDERATIONS

For best results, refer to the *i-STAT PT*^{plus} cartridge IFU for testing pre-requisites, limitations and precautions. When performing the performance verifcaiton across the reportable range consider the following:

DO

- **DO** include samples within the clinically relevant range as decided by the Laboratory Director.
- **DO** use one lot number of cartridges in the performance verification and ensure that cartridges and analyzers are at room temperature prior to testing.
- **DO** follow instructions for use for storage and handling of the cartridges, materials or samples to ensure accurate results. Improper preparation and use of the cartridge and samples may cause discrepant results or quality check codes.

DO NOT

- **DO NOT** improperly store cartridges. Using an *i-STAT PT*^{plus} cartridge that has not come to room temperature or is outside the 14-day room temperature expiration date may result in generation of quality check codes or unexpected test results.
- **DO NOT** incorrectly handle and fill the cartridge as this may generate quality check codes.

RECORDS AND RETENTION

It is the responsibility of the Laboratory Director to review, approve and store all records associated with the study. The laboratory accreditor may have additional guidelines pertaining to the length of time the records are required to be stored.

PERFORMANCE VERIFICATION STUDY
PATIENT TEST QUICK REFERENCE

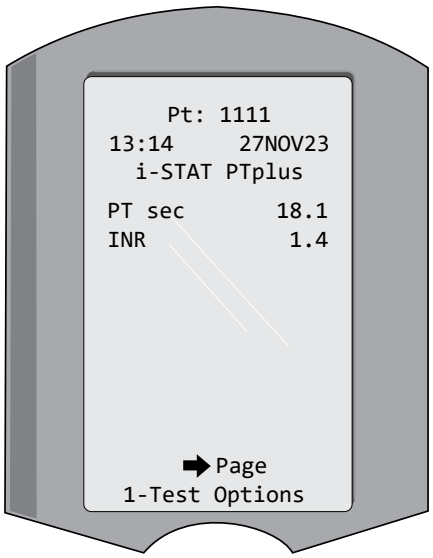
i-STAT 1 ANALYZER & *i-STAT PT*^{plus} CARTRIDGE

ANALYZER PATIENT TEST PROCEDURE OVERVIEW

The following is on overview of the testing procedure and not intended as training. Prior to performing the method comparison study, the Laboratory Director is responsible for ensuring that personnel have been trained to the *i-STAT* System. For testing details, refer to the *i-STAT PT*^{plus} cartridge IFU.

To perform a patient test with the *i-STAT 1* analyzer:

1. Press the power button to turn on the analyzer.
2. Press 2 (i-STAT Cartridge).
3. Follow the analyzer prompts.
4. Scan or Enter Patient ID. Enter or scan the sample id.
5. Scan the lot number on the cartridge pouch barcode.
6. Continue normal procedures for preparing the sample and filling and sealing the cartridge.
7. Push the sealed cartridge into the analyzer's cartridge port until it clicks into place. Wait for the test to complete.
8. Review results. Image below provides an example of a patient test result displayed by the analyzer.



REPEAT TESTING

If a result is outside the acceptable range for the sample used; repeat testing may be difficult due to the nature of coagulation testing. i.e the sample in the vial will have clotted. It is the Laboratory Director's discretion on what action to take for proficiency samples that are out of range.

CARTRIDGE HANDLING AND FILLING REMINDERS

CARTRIDGE HANDLING

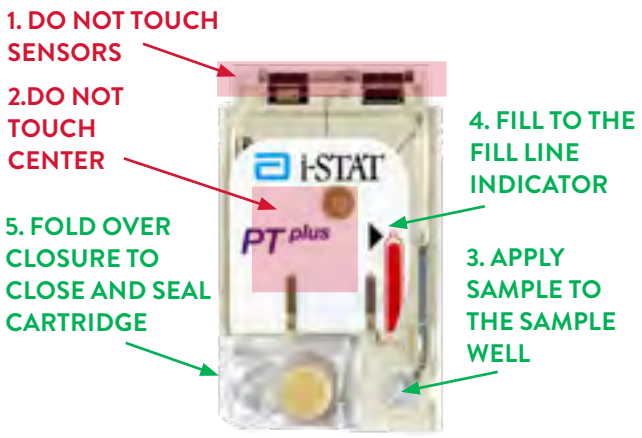
Cartridges and analyzers must be at room temperature prior to testing to prevent environmental quality check codes.

- Cartridge pouch - 5 minutes
- Cartridge Box - 1 hour
- Analyzer - 30 minutes

To prevent quality check codes related to mishandling of the cartridge, ensure that the sensors and center area of the cartridge are not touched. Cartridges should also be placed on a level, clean, non-fibrous surface, free of debris.

FILLING THE CARTRIDGE

To prevent quality check codes related to incorrect filling of the cartridge, fill the cartridge to the fill line indicator. Once filled, ensure that the cartridge is sealed.



PRECISION STUDY

"Precision" is defined in two different ways: (1) the degree to which the same method produces the same results on repeated measurements, and (2) the degree to which values cluster around the mean of the distribution of values.[8] Imprecision (standard deviation (SD), % coefficient variation (CV)) is the statistical expression of the differences between these measurements. The precision study should be performed over at least two days to satisfy CLIA 493.1253 (b)(1)(i) requirements.

PRECISION STUDY CONSIDERATIONS

The laboratory is responsible for verifying that it can repeatedly test the same samples under different conditions and get the same or comparable results (reproducible), regardless of which member of the laboratory's testing personnel performs the test (operator variance).[6]

TESTING CONSIDERATIONS

For best results, refer to the *i-STAT PT*^{plus} cartridge and *i-STAT PT*^{plus} *Control* Level 1 and Level 2 IFUs, for testing pre-requisites, material handling, limitations and precautions. When performing the precision study consider the following:

DO

- **DO** use one lot number of controls and cartridges in the study.
- **DO** test both levels of *i-STAT PT*^{plus} *Control* Level 1 and Level 2 a minimum of twenty (20) times over at least two days.
- **DO** follow instructions for handing the controls exactly to ensure accurate results. Only one vial of control should be reconstituted at a time and must be used in less than 30 seconds. With practice, multiple cartridges can be filled and inserted within 30 seconds.
- **DO** perform the control test using the quality control pathway on the *i-STAT 1* analyzer.

DO NOT

- **DO NOT** test less than 20 times for both levels of *i-STAT PT*^{plus} *Controls*. A minimum of 20 results for each level is recommended for proper statistical analysis.
- **DO NOT** test control material in the patient test or cal/ver test pathway on the *i-STAT 1* analyzer.

i-STAT PT^{plus} CONTROLS

The *i-STAT PT*^{plus} *Control* Level 1 and Level 2 are intended for use with the *i-STAT PT*^{plus} cartridge on the *i-STAT* System, and values assigned to these controls may not be commutable with other commercial methods.[26]

VALUE ASSIGNMENT SHEETS (VAS)

Abbott recommends documenting the Value Assignment Sheet information for the control level and cartridge lot used in the study.

Value Assignment Sheets are available on the APOC website, www.globalpointofcare.abbott. The sheet may be printed out and stored with the records of your method evaluation.

PT AND INR RESULTS

Abbott recommends recording the PT (seconds (sec)), whether or not your laboratory reports the PT (sec) for patient results. Recording the PT(secs) may help in troubleshooting unexpected results.

Your laboratory may customize the analyzer once the method evaluation has been completed, to disable the reporting of PT(secs), per your laboratory policy or procedure.

PRECISION STUDY CONTINUED

ACCEPTABILITY OF RESULTS FOR PRECISION STUDY

When reviewing results, the control result is considered acceptable when it is within the range specified in the Value Assignment Sheet.

If an out-of-range result is obtained and it can be confirmed that the cause was operator error, the result can be discarded and replaced with a result from a new cartridge. If more than one out-of-range result is obtained, the operator should review and practice the procedure.

The Laboratory Director has discretion on whether to discard additional out-of-range results and the continuation or restart of the precision study. It is best practice to ensure that decisions about out-of-range results in the precision study are documented in the method evaluation record.

PRECISION STUDY COMPARISON

Per the *i-STAT PT*^{plus} IFU, a multiday precision study was performed with *i-STAT PT*^{plus} control fluids and was based upon guidance provided in *CLSI EP05-A36*.[18] Duplicates of each fluid were tested twice a day for 20 days. The averaged statistics for total (within laboratory) precision (SD, standard deviation) are represented in the table within the IFU. SD and %CV are typical of current performance; however, results in individual laboratories may vary from this data.

The precision data provided in the *i-STAT PT*^{plus} cartridge IFU is representative of the data submitted to the FDA. It is not intended to be used as part of assessing the acceptability of your precision study.

VALUE ASSIGNMENT SHEET COMPARISON

i-STAT PT^{plus} *Control* Level 1 and Leve 2 Value Assignment Sheets only provide the mean and the range. They are also not intended to be used as part of assessing the acceptability of your precision study.

PRECISION STUDY DATA COLLECTION WORKSHEET

As an optional aid for customers, a worksheet is provided to collect data related to the precision study.

This worksheet helps ensure that all the device information is captured, along with control lots and replicate results.

PRECISION STUDY
CONTROL TEST QUICK REFERENCE

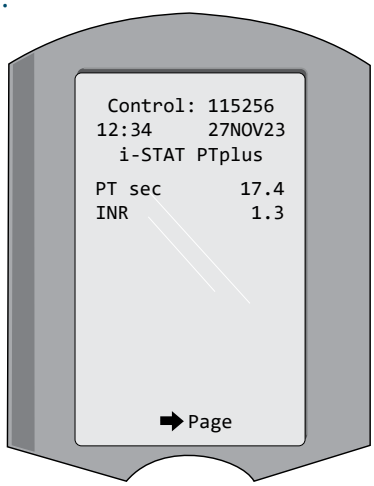
i-STAT 1 ANALYZER & *i-STAT PT*^{PLUS} CARTRIDGE

ANALYZER CONTROL TEST PROCEDURE OVERVIEW

The following is on overview of the testing procedure and not intended as training. Prior to performing the method comparison study, the laboratory director is responsible for ensuring that personnel have been trained to the *i-STAT* System. For testing details, refer to the IFUs for *i-STAT PT*^{plus} cartridge and *i-STAT PT*^{plus} *Controls*.

To perform a patient test with the *i-STAT 1* analyzer:

1. Press the power button to turn on the analyzer and the menu buuton to access the Administration Menu.
2. Press 3 (Quality Tests) and then 1 (Control).
3. Follow the analyzer prompts.
4. Scan or Enter Control Lot Number from the vial.
5. Scan the lot number on the cartridge pouch barcode.
6. Continue normal procedures for preparing the controls and filling and sealing the cartridge.
7. Push the sealed cartridge into the analyzer's cartridge port until it clicks into place. Wait for the test to complete.
8. Review results. Result is considered acceptable when it is within the range provided for that level in the VAS/eVAS. Image below provides an example of a control test result displayed by the analyzer.



REPEAT TESTING

If a result is outside the acceptable range provided in the Value Assignment Sheet (VAS or eVAS); repeat testing may be difficult due to the nature of coagulation testing. A new vial and cartridge must be used. The Laboraotry Director has discretion on addressing out-of-range result data in the study.

CARTRIDGE HANDLING AND FILLING REMINDERS

CARTRIDGE HANDLING

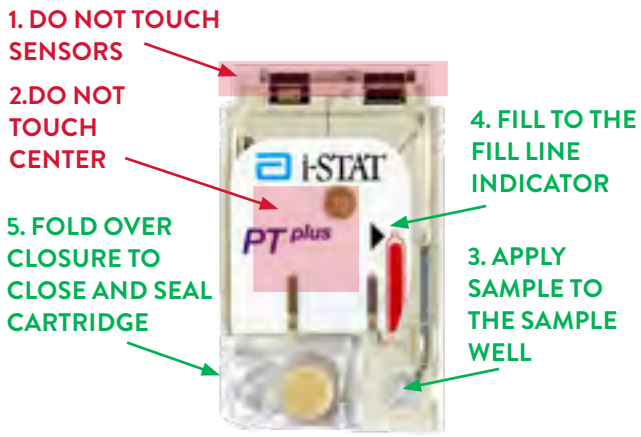
Cartridges, controls and analyzers must be at room temperature prior to testing to prevent environmental quality check codes.

- Cartridge pouch - 5 minutes
- Cartridge Box - 1 hour
- *i-STAT PT*^{plus} *Controls* (Level 1 and 2) vials - minimum of 45 minutes and maximum of 4 hours.
- Analyzer - 30 minutes

To prevent quality check codes related to mishandling of the cartridge, ensure that the sensors and center area of the cartridge are not touched. Cartridges should also be placed on a level, clean, non-fibrous surface, free of debris.

FILLING THE CARTRIDGE

To prevent quality check codes related to incorrect filling of the cartridge, fill the cartridge to the fill line indicator. Once filled, ensure that the cartridge is sealed.



PRECISION STUDY
DATA COLLECTION WORKSHEET

No.	Level 1	Level 2	Notes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

i-STAT 1 ANALYZER	
Serial Number:	
CLEW:	

i-STAT PT^{plus} CARTRIDGE	
Lot Number:	
Expiration Date:	

i-STAT PT^{plus} CONTROL LEVEL 1	
Lot Number:	
Expiration Date:	

i-STAT PT^{plus} CONTROL LEVEL 2	
Lot Number:	
Expiration Date:	

REVIEWED BY (PRINT NAME): _____

SIGNATURE AND DATE: _____ **PAGE :** _____ **OF** _____

VERIFICATION OF ADDITIONAL OR REPLACEMENT ANALYZERS

Abbott does not have manufacturer's requirements for testing liquid quality controls. Abbott offers the following suggestions for the Laboratory Director's consideration when verifying new or replacement analyzers:

PRECISION STUDY

Test two levels of control samples for each test that will be performed on a new or replacement analyzer.

Results must be within the acceptable range(s) on the Value Assignment Sheet(s). Store the Value Assignment Sheet(s) with the data as evidence that results were within acceptable limits.

In cases where available control materials do not span the reportable range, patient samples with known values can be used to expand the verified range.

ACCURACY

Use the data from the method comparison (for accuracy) study to assess accuracy. In addition, test one or more patient samples on the new or replacement handheld and a comparative method or on a previously verified *i-STAT* device.

The difference(s) between the new or replacement device and the comparative method or previously verified device should not exceed the laboratory's required level of agreement between systems.

REFERENCE INTERVALS

Use the reference intervals established at the time of the initial verification. The reference ranges programmed into the analyzer and found in the IFU are intended as guides for interpreting results. Since reference ranges can vary depending on demographics such as age, sex, race and ethnicity, it is recommended that reference ranges be determined by the facility and approved by the Laboratory Director.

REFERENCES

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