Hotspot Clinical Pipeline  
Version 3.0

Validation Project Plan (VPP)

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# OVERVIEW

## PRE-APPROVAL

Signing this plan indicates that the contents of this document have been reviewed and accepted. The following responsible functional areas have approved this plan:

**Approved By:**  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Business Owner/Designee Date

**Approved By:**  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Dir of Bioinformatics/Designee Date

**Approved By:**  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Quality Assurance Date

**Approved By:**  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Clinical Lab Director/Designee Date

# INTRODUCTION

## BACKGROUND

In order to be able to accommodate future assays and panels sold by ThermoFisher Scientific, the IonTorrent Software Suite (including operating software for some clinical instruments, research instruments, and cluster hardware) must be upgraded from version 5.0.2 to version 5.4. These software upgrades will necessitate modifications to in-house developed software including the variant calling pipeline, data loading pipelines, and the clinical dashboard.

## SUMMARY

This Validation Project Plan describes the tasks and deliverable documentation associated with modification of the Hotspot Clinical Pipeline with current expectations of regulatory agencies and Sema4-CT computer system validation policy. When completed, this validation project will provide documented evidence, to a high degree of assurance, that the system will accurately and reliably perform the functions intended for use in the environment in which it is installed.

Specifically the validation plan defines:

* Responsibilities and tasks of persons responsible for execution.
* The validation approach.
* Validation tasks necessary for providing documented evidence that the system performs its various functions correctly and consistently.
* Validation deliverables.

## GLOSSARY

|  |  |
| --- | --- |
| **Term** | **Definition** |
| CAP | College of American Pathologists |
| CLIA | Clinical Laboratory Improvement Amendments |
| CT | Connecticut |
| GLP | Good Laboratory Practice |
| Sema4-CT | Sema4 Laboratory located in Branford, Connecticut |
| NY | New York |
| SME | Subject Matter Expert |
| SRS | Software Requirements Specification lists the software features required by users of the system |
| TRS | Technical Requirements Specification describes the hardware at a technical level |
| V&V | Verification and Validation |
| V&VP | Verification and Validation Protocol, the test cases for the V&V |
| VPP | Validation Project Plan |
| VSR | Validation Summary Report |

# TEST ENVIRONMENT

The Hotspot Clinical Pipeline encompasses the hardware and software running on three different servers: 1) Torrent Cluster, 2) BigIron server, and 3) Dashboard server. The software on the Torrent Cluster will be tested by Lab and Bioinformatics personnel completing several sequencing runs based on the Clinical Hotspot template using the Torrent Suite interface located at the following address: http://10.93.132.23/data/#table. The software on the BigIron server will be tested by Bioinformatics personnel running the scripts for variant calling and data import for the validation runs output by the Torrent Cluster. BigIron is located at the following ip address: 10.93.132.63. The software on the Dashboard server will be tested by Clinical Directors using Google Chrome to utilize the Hotspot Clinical Dashboard to process the samples from the validation runs. The Hotspot Clinical Dashboard test instance is located at the following address: http://10.93.132.25:9090/login.

# ROLES AND RESPONSIBILITIES

## Sema4-CT Testers

The following SMEs will be utilized for testing:

* Bioinformatics personnel (V&V)
* Lab personnel
* Clinical Directors

## APPROVAL OF DELIVERABLES

The approval of deliverable documentation as defined in section 7 will be made by:

* Business Owner
* Clinical Lab Director
* QA Lead
* Bioinformatics Lead

## Sema4-CT RESPONSIBILITIES

* Finalize validation requirements
* Author and execute PQ
* Review and sign off on Error Resolution forms
* Finalize validation summary report

## OTHER RESPONSIBILITIES

* ThermoFisher Scientific personnel will upgrade the Torrent Cluster, Ion sequencers, and Ion chefs to version 5.4

# SYSTEM DESCRIPTION

The hardware is described by the Technical Requirements Specification.

# VALIDATION ACTIVITY REQUIREMENTS

## VALIDATION METHODOLOGY

The following sub-sections describe the methodology utilized to validate the system.

### 6.1.1 VALIDATION PROJECT PLAN

A Validation Project Plan [this document] defines the scope of work (activities and deliverables) required to validate a system, and identifies the design documents that will form the basis for: Design, Installation and Validation and Verification. The VPP will describe the project, the system and the sequence of validation activities within the project.

### 6.1.2 DESIGN QUALIFICIATIONS

Software Design documentation for Torrent Suite 5.4 reside at http://10.93.132.23/ion-docs/GUID-862A6B7B-6BB8-47AB-892F-4F5F9F2D4130.html and include software specifications and release notes.

Design qualifications for previous versions of the Hotspot Clinical Pipeline are found in the Software Requirements Specification (SRS) and Appendix 2 of this document. Design qualifications for changes made in this version of the Hotspot Clinical Pipeline are found in the User Requirements Specification (URS) and can also be found in the Sema4 JIRA instance under the Hotspot Clinical Software project.

### 6.1.3 SOFTWARE REQUIREMENTS SPECIFICATION (SRS)

#### Clinical Pipeline Database (CPD)

All CPD data is stored in a custom MySQL database. The in-house Dashboard software provides front-end access to the Clinical Pipeline database. Front-end access is traceable and is based on privilege; this access system is controlled via user’s active directory domain accounts. There are three levels of users: (1) System Administrator, (2) Clinical Laboratory Director and (3) Laboratory Technician.

The Clinical Pipeline database stores the following types of information

1. Run and sample level quality control and metadata imported from the sequencing system
2. Sample data imported from the LIMS
3. Variant results for all samples run through the sequencing system
4. Fluidigm and reference control sample expected result lookup tables and results from the sequencing system runs
5. Panel level information including amplicon coordinates
6. Annotation information including data from public databases such as Refseq, Entrez Gene, COSMIC, ExAC, and ICGC, commercial databases such as ICMDB, and in-house generated annotation data
7. Confirmation results for selected variants generated using secondary assays (e.g. Sanger, qPCR)
8. Clinical report data including data on revisions
9. Permission level authorization for individual user accounts
10. Logging information which captures the user account performing the action, a timestamp of the action, and a description of the action such as data import or workflow actions taken with the Dashboard front-end

#### Fluidigm Import

A program script that loads result files output from a Fluidigm custom assay directly into the Fluidigm expected results table in the Clinical Pipeline database.

#### Clinical Import

A program script that does the following steps in succession

1. Uses Application Program Interfaces (APIs) to import into the Clinical Pipeline database specific run-level and sample-level quality metrics that are generated by the Torrent Suite Analysis Pipeline and Plugin software during sequencing and data processing. Torrent Suite software processes each sequencer run in multiple steps including signal processing, base calling, read filtering, alignment QC and coverageAnalysis plugin. The quality metrics generated by the Torrent Suite software are stored in files on the Torrent Cluster backend and summary data are reported in Torrent Browser.
2. Uses APIs to import sample metadata from the Core LIMS Oracle database into the Clinical Pipeline database.
3. Calls the appropriate variant caller depending on the panel/test and imports the called variants into the Clinical Pipeline database.
4. Uses the imported data from the variant caller and the Fluidigm assay to determine the Control QC Status and Identity QC Status for each sample and import the results into the Clinical Pipeline database. Specifics for this step are described in greater detail in a following section.

Once the QC status calculation and the variant calls for the genetic test are imported into the Clinical Pipeline database all intermediate files (such as VCF files) are deleted. The only variant data that will be retained is that for the variants covered by the specific genetic test ordered.

#### Quality Control Processing

1. Sequencing QC

Based on sequencing quality metrics imported from the Torrent Cluster and stored in the Clinical Pipeline database a sample will pass or fail. These metrics are: Mapped Reads, Mean Depth of Coverage, Reads on Target, and Uniformity. Quality metrics for all samples are manually reviewed. Sequencing quality control summary results and detailed data for each sample are displayed on the Sample QC page of the Dashboard. Each sequencing run records the identification number of the individual sequencer instrument used for that run so that quality control audits can be performed.

1. Control QC

Control samples for the specific genetic test will be run on each sequencer chip that includes samples interrogated for that test. The control QC procedure compares the variant calls made based on the sequencing data to the known variant calls for those samples. For samples on a sequencer chip to pass control QC there must be 100% concordance between the variant calls for all control samples on the same sequencer chip and the known calls for those coordinates. Concordance includes variant calls and reference calls at each genomic coordinate.

1. Identity QC

Two independent genomic DNA extractions are performed on each sample queued for a clinical genetic test. One extraction is used for the genetic test based on NGS DNA-Sequencing; the other extraction is used for Identity QC by genotype at a number of SNP positions determined using the Fluidigm SNP Trace platform. Genotype calls produced using the genotyping platform are exported from the Fluidigm Genotype Call software as a text file. The genotype calls are imported into the Clinical Pipeline database using the Fluidigm Import script mentioned previously. Genotype calls based on the results of the sequencing system are produced by the Germline Variant Caller standalone Torrent Variant Calling pipeline (TVC) and imported into the Clinical Pipeline database using the Clinical Import script. For each sample, the genotype calls based on Fluidigm assay are compared with the genotype calls based on sequencing output to calculate concordance between the two platforms. The sample concordance is imported into the Clinical Pipeline database. A sample passes Identity quality control if the concordance between the two platforms for that sample is greater than or equal to a specified percentage. A sample with a concordance call below the threshold specified in the test-specific SOP will fail Identity QC.

#### Variant Caller

The Germline or Somatic Variant Caller calls variants based on the sequencing data from the Torrent Cluster, allows for quality control review and quality control gating, and makes these data available for Clinical Laboratory Director or Pathologist approval and reporting. Much of the germline or somatic variant caller operates in an automated fashion. The decision to use the Germline or Somatic Variant Caller is made based on what type is called for in each specific test.

1. The Germline Variant Caller calls variants from the bam files with the Standalone Torrent Variant Calling (TVC) pipeline including a Combined Hotspots file. This hotspots file specifies the variants used for identity quality control and the specific variants that are being interrogated by the genetic test specified for the sample. Using TVC parameters specified in TVC parameter file, the TVC calls separately, SNPs, short indels and long indels and force calls variants at the genomic coordinates specified in the Hotspots file. These files are merged to produce the TVC output vcf file. This TVC output vcf file is filtered against a HotSpots.bed file (which contains the coordinates for all variants specified in the combined HotSpots file) to generate a vcf file that reports calls and statistics for only the coordinates of the combined hotspots files. The data for the genetic panel variant coordinates are imported into the Clinical Pipeline database.
2. The Somatic Variant Caller calls variants from the bam files with the Somatic Combo Variant Caller (Combo) pipeline. The Somatic Combo Variant Caller integrates stand-alone TVC 5.4 variant caller, Scalpel 0.4.1 INDEL caller, Burrows-Wheeler transformation (BWA) 0.7.5a-r405 and CDHIT-454 error correction tool to make a variant calling pipeline. The raw variants from TVC or Scalpel are filtered and left-aligned and are combined into single Combo VCF file per sample. The variants from the Combo VCF file are imported into the Clinical Pipeline database by the previously mentioned Clinical Import script.

#### Dashboard

The Dashboard is a graphical user interface that allows appropriate personnel, based on login and privilege to view sample data and to promote samples through the review workflow.

The Dashboard consists of five pages which make up the major workflow steps in the Clinical Pipeline as well as eight secondary pages that provide additional functionality. The five major pages include Sample QC, Variant QC, Variant Annotation, Report Configuration, and Report Generation. The eight secondary pages include Requeue List, Withdrawn List, Sanger Confirmation List, qPCR Confirmation List, Samples Processing List, Samples Reported List, Total Samples List, and Admin Control. Each page along with other Dashboard features is discussed in detail below.

1. Portal Page

Upon first logging in to the Dashboard the user is presented with the portal page which lists all available tests/panels. By clicking on the link for a specific test/panel the user will be brought to a version of the Dashboard with specific functionality for that test/panel.

1. Sample QC

The Sample QC page shows all samples at the sample quality control clinical pipeline workflow step. This step involves checking each sample for acceptable sequencing quality control metrics, control samples matching expected results, and positive identity matching between sequencing results and Fluidigm assay results. For each sample the page shows sample name, barcode, and received date, DNA input as concentration and absolute mass, sequencing metrics such as number of mapped reads, on target percent, minimum read depth, uniformity, and percent failed amplicons, the results of the three quality control tests (sequencing, control, and identity), a link to the run information page for this sample in the Ion Torrent Suite software, and the number of times this sample has been repeated. The user is able to comment on each sample, and can either pass the sample to the next step (Variant QC), fail the sample which sends it to the Requeue List, or withdraw the sample which sends it to the Withdrawn List.

1. Variant QC

The Variant QC page shows all samples that have passed sample quality control including sequencing QC, control QC, and identity QC and are now at the variant quality control clinical pipeline workflow step. This step involves reviewing each variant for each sample and determining if the variant should be reported, ignored, or confirmed with a different assay technology. Any variants that fail result in that sample failing and being sent to the Requeue List. For each variant in a sample the page shows the gene, chromosome number, genomic position, reference and alternate alleles, cDNA and amino acid change notation (which is only populated if that variant already exists in the database), allele frequency, coverage at that position, variant quality score, strand bias, whether the variant is positive, negative, or inconclusive based on the coverage and allele frequency statistics, the status of the variant (pending, passed, failed, ignored, confirmation), the results of the sanger or qPCR confirmation assays, a set of links to external database websites, and the user that reviewed and timestamp of review. Once the user has passed or ignored all variants for a sample, that sample will then move to the next step in the workflow which is Variant Annotation.

1. Variant Annotation

The Variant Annotation page shows all samples that have passed variant quality control (all variants were passed or ignored) and are now at the variant annotation clinical pipeline workflow step. This step involves reviewing each variant for each sample and determining an associated transcript, editing the annotation if necessary, and selecting the variant clinical significance tier (unreported, a variant of uncertain significance, director override, a tier 2 clinical variant, or a tier 1 clinical variant). For each variant in a sample the page shows an annotation link which either allows the user to either edit existing annotation (from public or commercial databases) or add a new annotation entry, the gene, chromosome number, genomic position, reference and alternate alleles, the assembly the sample was mapped against, a link to select the transcript for that variant which then auto-populates the CDS start, exon, cDNA and amino acid change notation fields, allele frequency, whether the variant is positive, negative, or inconclusive based on the coverage and allele frequency statistics, a set of links to external database websites, and a selector indicating if the variant clinical significance tier. The user is also able to click on each variant to add variant specific comments. Once the user has entered and edited the annotation information to their satisfaction, they can then save the changes and send the sample to the next step in the workflow which is Report Configuration.

1. Report Configuration

The Report Configuration page shows all samples that have passed the variant annotation step and are now at the report configuration clinical pipeline workflow step. This step involves reviewing each variant for each sample and confirming that they are correctly annotated and grouped into the correct clinical significance tier. For each variant in a sample the page shows the gene, chromosome number, genomic position, reference and alternate alleles, the assembly the sample was mapped against, the selected transcript for that variant, the CDS start, exon, cDNA and amino acid change notation, allele frequency, whether the variant is positive, negative, or inconclusive based on the coverage and allele frequency statistics, a set of links to external database websites, and a selector indicating if the variant clinical significance tier. Once the user has confirmed the annotation information and the variant clinical significance tier to their satisfaction, they can then save the changes and send the sample to the next step in the workflow which is Report Generation.

1. Report Generation

The Report Generation page shows all samples that have passed the report configuration step and are now at the report generation clinical pipeline workflow step. This step involves reviewing a preview of the final report for accuracy and then signing off on the report so that it can be downloaded with the signature of the Clinical Director. By clicking on a sample the preview of the report is shown. The report includes a header with patient information including name, date of birth, reference number, test type, and indications if any, sample information including specimen type, lab number, date collected, and date received, and clinician information including doctor name, affiliation, and contact information. The results section of the report indicates how many genes were tested, the detected genomic alterations, a list of genes where alterations were not detected, a list of variants with direct clinical associations, a list of variants with possible clinical associations, and a list of variants with uncertain significance. The report also includes a methodology section explaining the process by which the sample was analyzed and the detection limits of the test. Once the user determines that the report is in a finalized state, they can click sign off to authenticate and add their electronic signature to the report which is now available for download.

1. Requeue List

The Requeue List page shows all samples that have failed during the Sample QC step or Variant QC step. This page allows users to view samples that need to be re-sequenced, download a list of those samples in CSV file format, mark the requeueing process as complete for each sample once re-sequencing has begun, or send a sample back to the Sample QC page. For each sample the page shows sample name, barcode, and received date, DNA input as concentration and absolute mass, sequencing metrics such as number of mapped reads, on target percent, minimum read depth, uniformity, and percent failed amplicons, the results of the three quality control tests (sequencing, control, and identity), a link to the run information page for this sample in the Ion Torrent Suite software, and the number of times this sample has been repeated. The user is able click on the return arrow in the first column to return a sample to the Sample QC page if it was failed by mistake or click on the download button at the bottom of the page to download a CSV format file with all sample information from the requeue list. For each sample for which re-sequencing is successfully started in the LIMS, the user can mark that sample as completed in the requeue list by clicking on the requeueing link and confirming that the sample requeue process is completed.

1. Withdrawn List

The Withdrawn List page shows all samples that have been withdrawn during the Sample QC step. This page allows users to view samples that have been withdrawn from testing for any reason after the sample has already been processed and entered the dashboard for analysis, download a list of those samples in CSV file format, or send a sample back to the Sample QC page. For each sample the page shows sample name, barcode, and received date, DNA input as concentration and absolute mass, sequencing metrics such as number of mapped reads, on target percent, minimum read depth, uniformity, and percent failed amplicons, the results of the three quality control tests (sequencing, control, and identity), a link to the run information page for this sample in the Ion Torrent Suite software, and the number of times this sample has been repeated. The user is able click on the return arrow in the first column to return a sample to the Sample QC page if it was withdrawn by mistake or click on the download button at the bottom of the page to download a CSV format file with all sample information from the withdrawn list.

1. Sanger Confirmation List

The Sanger Confirmation List page shows all sample-variant pairings that have been selected by the user to undergo confirmation with Sanger sequencing technology. This page allows users to view variants in the Sanger confirmation process, send the variants to be confirmed to the LIMS, download a list of those variants in CSV file format, update the status of each variant confirmation, and upload a document containing images of the Sanger chromatograms for each variant confirmation. For each sample-variant pair the page shows the sample name, receipt date of the sample, gene encompassing the variant to be confirmed, strand (positive or negative) of the gene, sequencing directions of the Sanger process, amplicon primer set that covers that variant, chromosome number, genomic position, reference allele, and alternate allele for that variant, variant status which includes PENDING (not yet sent to LIMS for processing), PROCESSING (sent to LIMS and currently undergoing the confirmation process), NTC Failure (the no template control sample failed during the confirmation process), Control Failure (the control sample(s) failed during the confirmation process), Samples Failure (the testing sample(s) failed during the confirmation process), Not Detected (the variant was not confirmed), and Detected (the variant was confirmed), a button that allows Sanger chromatogram uploading, and the number of times that sample-variant pairing has undergone Sanger confirmation. The user is able to mark sample-variant pairs that should be sent to LIMS and then click the “Send to LIMS” button at the bottom of the page to send them. This changes the status of each sample-variant pair to PROCESSING. The user is also able to click on the download button at the bottom of the page to download a CSV format file with all sample-variant information from the Sanger Confirmation list for manual processing in case the connection between the Dashboard and LIMS is disabled. Once results from the confirmation assay have been received the user is able to enter the results for each sample-variant pair by clicking on the status, selecting the appropriate choice, and clicking the check mark. Once results have been received the user should also upload images of the Sanger chromatograms by clicking the upload button for the sample-variant pair, clicking on choose file to select the file with the images, and then clicking upload. Setting the results of the confirmation assay on the Sanger Confirmation List page will automatically update the results on the Variant QC page allowing the user to then either pass, fail, or ignore the confirmed variant.

1. qPCR Confirmation List

The qPCR Confirmation List page shows all sample-variant pairings that have been selected by the user to undergo confirmation with qPCR technology. This page allows users to view variants in the qPCR confirmation process, send the variants to be confirmed to the LIMS, download a list of those variants in CSV file format, and upload a results file produced by Mutation Detector Software 2.0. For each sample-variant pair the page shows the sample name, receipt date of the sample, gene encompassing the variant to be confirmed, strand (positive or negative) of the gene, amplicon primer set that covers that variant, chromosome number, genomic position, reference allele, and alternate allele for that variant, qPCR assay name, variant status which includes PENDING (not yet sent to LIMS for processing), PROCESSING (sent to LIMS and currently undergoing the confirmation process), NTC Failure (the no template control sample failed during the confirmation process), Control Failure (the control sample(s) failed during the confirmation process), Samples Failure (the testing sample(s) failed during the confirmation process), Not Detected (the variant was not confirmed), and Detected (the variant was confirmed), and the number of times that sample-variant pairing has undergone qPCR confirmation. The user is able to mark sample-variant pairs that should be sent to LIMS and then click the “Send to LIMS” button at the bottom of the page to send them. This changes the status of each sample-variant pair to PROCESSING. The user is also able to click on the download button at the bottom of the page to download a CSV format file with all sample-variant information from the qPCR Confirmation list for manual processing in case the connection between the Dashboard and LIMS is disabled. Once results from the confirmation assay have been received in the form of an output file from Mutation Detector Software 2.0, the user is able to upload the results file using the Upload qPCR Results File button which opens a dialog to select the file to upload. This results file upload process will open a results summary screen that allows the user to set the variant confirmation statuses based on the qPCR results. Once these sample-variant confirmation statuses have been set the results on the Variant QC page are automatically updated. If necessary the user is able to enter the results for each sample-variant pair manually without uploading a results file by clicking on the status and selecting the appropriate choice. Once the confirmation results have been updated on the Variant QC page this allows the user to then either pass, fail, or ignore the confirmed variant.

1. Samples Processing List

The Samples Processing List page shows all samples currently in the Dashboard that are in Sample QC, Variant QC, Variant Annotation, Report Configuration, and Report Generation steps but have not yet had a report generated that was finalized and signed off by the clinical director. For each of these steps the Samples Processing List page shows for each sample whether the step was completed, which user the step was completed by, and the date and time that the step was completed. Clicking on the checkmark under the SampQced column shows the results of the Sample QC process and any comments entered for that sample. Clicking on the checkmark under the VarValid column shows the results of the Variant QC process for that sample. Clicking on the checkmark under the AnnotRevd column shows the results of the Variant Annotation process for that sample. Clicking on the checkmark under the Configed column shows the results of the Report Configuration process for that sample.

1. Samples Reported List

The Samples Reported List page shows all samples currently in the Dashboard that have had a report generated that was finalized and signed off by the clinical director. For each sample that has been reported the Samples Reported List page shows all of the same information as the Samples Processing List page and in addition shows that the sample has been reported, which user generated the final report, and the date and time the report was generated. Clicking on the checkmark under the Reported column shows the final report that was generated.

1. Total Samples List

The Total Samples List page shows all samples currently in the Dashboard regardless of their workflow step or whether they have been reported. It shows the same information as the Samples Processing List page and the Samples Reported List page.

1. Admin Control

The Admin Control page is only visible to users with the necessary permissions. It shows the user name of all users with accounts, the role of that user, and the date and time that the user last logged in. The user is able change the roles of any user in the system by selecting the use name from the first dropdown menu at the bottom of the screen, the role to assign to the user from the second dropdown menu, and clicking on the Confirm button.

1. Activity Logging and User Role Permissions

There is electronic tracking of identity and date/timestamp for all activity done using the Dashboard. This is done in the log table of the Clinical Pipeline database where an entry describing the specific action taken by the user, their user name, a timestamp, and optionally a comment regarding the action are generated each time any user performs an action. The types of actions that can be taken using the Dashboard are limited based on the role assigned to the user. There are three types of roles: System Admins, Clinical Directors, and Lab Technicians. System Admins can view any page and perform any action including viewing the Admin Control page and assigning users to different roles. Clinical Directors can view any page except the Admin Control page meaning they cannot assign users to different roles. Lab Technicians can view all pages except the Admin Control page but can only perform actions on the Requeue List Page, Sanger Confirmation List page, and qPCR Confirmation List page.

### 6.1.4 VALIDATION AND VERIFICATION (V&V)

A Validation and Verification Protocol will be prepared and executed by Sema4-CT prior to the software upgrade going live for clinical use. The V&V provides documented evidence that the system functions according to the system Software Requirements Specification.

The strategy for the test V&V includes the following components:

* Critical end-to-end workflow testing (PQ Scripts)
* Sema4-CT-specific configuration requirements that are present in the SRS and URS
* Sema4-CT interface testing
* At-risk regression testing of components
* Tests of used features from the newest release that are present in the URS

A recent copy of the production system will be validated during V&V, which will be performed according to pre-approved test plans with defined acceptance criteria. The conclusions of the V&V will be documented in the Validation Summary Report.

### 6.1.5 VALIDATION SUMMARY REPORT

All tests will be traceable to requirements [and other specified features] in this report through a Traceability Matrix. After the V&V protocol has been executed, the results of the testing along with resolution of any errors will be summarized in a Validation Summary Report (VSR).

The report will also document any errors, constraints or limitations that have been placed on the production use of the system and any corrective actions that must be completed before the system can be utilized in production. The system will be installed in the production environment.

The VSR will include or reference a list of corrective actions that are required to be addressed. These will be reviewed prior to approval of the VSR and a process established to manage the actions to completion.

Each error is associated with a priority for resolution as follows:

|  |  |
| --- | --- |
| **Priorities** |  |
|  | Definition |
| High | The issue poses a significant risk to patient reporting outcomes. |
| Medium | The issue poses a low risk to patient reporting outcomes. |
| Low | There is no risk to patient reporting outcomes (such as a cosmetic change). |

Validation will begin execution on 29 SEP 2017. If no high priority issues are discovered during the test, the report will be authored by 09 OCT 2017.

# ASSUMPTIONS, EXCLUSIONS, AND LIMITATIONS

## COMPLIANCE REQUIREMENTS

Compliance will be achieved if the validation requirements as described within Section 5.0 - Validation Activity Requirements have been fulfilled.

Validation of the system and related components will be based on compliance requirements referenced as GLP, CAP, CLIA and any other applicable regulations. The core validation effort will consider requirements specifically as regulated by the US Code of Federal Regulations.

# PROJECT VALIDATION ORGANIZATION

The team identified for this project is comprised of Sema4-CT QA, Bioinformatics personnel and Clinical directors.

The team responsibilities as defined below are to:

* Define the validation standards
* Develop, maintain and communicate the validation plan
* Create detailed definition of validation tasks
* Develop review and/or maintain Protocols, Test Plans and Test Cases as necessary
* Co-ordinate, guide, evaluate, assist, and monitor progress of validation
* Assign responsibilities for validation in accordance with the standard operating procedures
* Ensure project compliance though reviews, audits, etc.
* Recommend, as necessary, the formation of additional validation teams
* Consider and apply appropriate standards, including regulatory expectations
* Work with the software suppliers and consultants, as required for successful validation
* Develop, maintain and communicate the validation summary report.

# VALIDATION DOCUMENTS REQUIRED

The following is a list of validation deliverables.

| **Deliverables** |
| --- |
| **Validation Project Plan** |
| **User Requirements Specification** |
| **Technical Requirements Specification** |
| **Clinical Pipeline Change Form(s)** |
| **Performance Qualification - PQ** |
| **Validation Summary Report** |

# ACCEPTANCE CRITERIA

The system will be deemed acceptable when the Validation Summary Report has been satisfactorily completed and approved and it states that the system is in a validated state. The approval of the VSR includes the following criteria:

* The process of case migration has been confirmed within the test environment such that assurance is demonstrated for production.
* It has been demonstrated that the Software Requirements, as defined in the Software Requirements Specifications, have been satisfied including that the system performs reproducibly and consistently within its full range of operating functionality.
* All known critical problems are documented and resolved through software fixes or workarounds as applicable.
* Any constraints concerning the release of the system to production are documented.
* All essential documents have been adequately produced, reviewed, and approved.

**VERSION HISTORY**

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| --- | --- | --- | --- |
| **Date** | **Version** | **Description of Document Updates** | **Author** |
| 18 SEP 2017 | 1.0 | Initial Version | Jonathan Keeling |
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# APPENDIX 1: VALIDATION TESTING ERROR AND RESOLUTION REPORT

The Systems Validation Report and Resolution Form is designed to track and analyze malfunctions of software and computer systems as well as serious events or near misses which might have resulted in interruption of work flow or inability to meet industry standards. All occurrences and events shall be reported in order to establish a written record of factors which caused deviation from the standard as well as maintain a capability to promptly investigate occurrences in order to initiate and support corrective and/or preventive action.

A Systems Validation Report and Resolution Form (see example below) will be completed by any individual having personal knowledge of an occurrence. This form is designed to be used for software/system malfunctions or other occurrences that require documentation. Once the form has been completed, the original should be attached to the test protocol executed there under for record keeping. A Downloadable fillable Validation Testing Error and Resolution Report.pdf is available from Master Control MSGTL-CT-QA-FORM-0048.

**Validation Testing Error Report and Resolution Form**

**Test Number:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ **Error Number:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Name of System: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Date of Error: \_\_\_\_\_\_\_\_\_\_\_\_ Time of Error: \_\_\_\_\_\_\_\_\_\_\_\_ Date of Report: \_\_\_\_\_\_\_\_\_\_\_\_**

**Description of Error:** (Please include what happened, where it happened, how it happened if known, attach additional sheets for space as needed, and attach screenshots)

**Cause/Impact:**

**Investigation/Proposed Resolution:**

**Reported to: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Signature of Person Making Report: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Implemented Resolution:**

**Report Reviewed and Approved: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**QA Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

# APPENDIX 2: Project design documentation for the Hotspot Clinical Pipeline v3.0 and confirmation process



