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CRAB
Cancer Research And Biostatistics

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Prepared for the Canadian Cancer Trials Group:

This correspondence is in response to your request for validation and security information related to SWOG registration trials that utilize SWOG and National Cancer Institute (NCI) systems. This documentation can be used to attest the effort made by SWOG to establish and maintain systems in compliance with regulatory requirements. This information covers all SWOG registration trials hosted on Medidata Rave that must meet the requirements of the Food and Drug Administration under 21 CFR Part 11.

Information on the following areas is included, as requested:

- Validation Process Summary for the SWOG Medidata Rave EDC
- System Security Verification for the SWOG Statistics and Data Management Center (SDMC)
- Information on Security and Validation for NCI Support Systems

Validation Process Summary for the SWOG Medidata Rave EDC

SWOG FDA registration trials are hosted on cloud-based Medidata systems that provide a secure platform for electronic case report forms (eCRFs) in an electronic data capture (EDC) system. These trials include, but are not limited to, S1404, a National Cancer Institute (NCI)-sponsored SWOG-coordinated clinical Phase III Randomized Trial Comparing High Dose Interferon to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma. This also includes S1605, also an NCI-sponsored SWOG-coordinated clinical trial. S1605 is a Phase II Trial of Atezolizumab in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer.

Medidata Rave is fully validated and compliant with 21 CFR Part 11. This is documented in the Medidata Rave Regulatory Compliance Summary named OTHER-QA-004-08 pages 108-118, and the iMedidata Regulatory Compliance Summary named OTHER-QA-009-01 pages 26-37. These documents are under confidentiality with Medidata and cannot be disseminated. They are available for review through the Regulatory/Quality Assurance Manager at Cancer Research And Biostatistics (CRAB).

SWOG FDA registration trials require a customized Rave study build and the support of the SWOG database. The following SOPs describe the customized software development and validation processes that are being followed for developing these components.

- APD012: Software Development Lifecycle
- APD007: Software Developer and User Testing
- APD009: Coding Standards
- APD010: Source Code Version Control

- DAM001: Rave Study Build Process
- DAM002: Study Metadata Entry and Maintenance
- ADM005: Change Control for Qualified and Validated Computerized Systems

The Software Development Lifecycle SOP requires the following documents to cover full validation of FDA registration trials, including S1404 and S1605, and customizations.

- User Requirements
- Project Plan
- Functional Specifications
- Risk Analysis
- Technical Specifications
- Code Review Plan
- Build Notes
- Developer Testing
- User Testing Protocol
- User Testing Report
- User Acceptance Testing
- Installation Protocol
- Installation Report
- Release Notes
- System Release Report

This documentation was completed for S1404 in 2015 and S1605 in 2017.

Minor version changes such as additions of eCRFs or superficial user interface updates will follow the procedures outlined in the Change Control SOP. Validation deliverables are updated as appropriate.

System Security Verification for the SWOG SDMC

We have attached the SWOG system security description – SWOG System Security Verification v.2 (7/20/2015) – that was created for federal Veterans Affairs and Department of Defense patient care facilities that require compliance with Federal Information Security Management Act (FISMA) 2002 requirements. In addition, SWOG conducts an annual Compliance Assessment to review systems that we consider to be in scope. Those systems include the database and associated systems at the SDMC and SWOG's Medidata-hosted Rave implementation. The most recent Compliance Assessment is attached. Updates are posted at www.swog.org.

Information on Security and Validation for Key NCI Support Systems

NCI support systems used in support of SWOG trials include:

- Rave EDC from Medidata
- TRIAD (Transfer of Images and Data) from Imaging and Radiation Oncology Core at the American College of Radiology
- Oncology Patient Enrollment Network (OPEN) from the Clinical Trials Support Unit (CTSU)

Validation of these NCI-provided systems does not fall under SWOG's responsibility. The trials that are deployed within Medidata Rave are validated, as described above. Medidata validates the base EDC system.

Rave EDC from Medidata

Upon implementation of Medidata Rave for NCI trials, Medidata provided the networks with the validation noted above. The documents cover the validation process for the Rave EDC and the login application which is supported through iMedidata.com. As noted, these documents can be reviewed at CRAB. As a summary of Medidata validation and security practices, we have included the Medidata Clinical Cloud (MCC) Validation Fact Sheet from September, 2016, which can be viewed online at https://www.mdsol.com/sites/default/files/MCC_MCC-Validation_201509_Medidata_Factsheet.pdf (copy attached).

On-site audits of Medidata Rave were conducted in 2011 by the National Institutes of Health (NIH) Rave Validation Working Group, Site Audit Committee. Under the organizational guidance from Westat, representatives from the NIH and the NCI Oncology Cooperative groups (including staff from the SWOG SDMC) audited Medidata development and cloud-hosting locations.

TRIAD Imaging

The Transmission of Imaging and Data (TRIAD) system is a standards-based system built by the American College of Radiology (ACR) for the seamless exchange of images and data for accreditation, clinical trials and registries. TRIAD is integrated with the RSS database for authentication, and with Rave to populate lists of patients enrolled on trials, and time points at which images are expected to be submitted. DICOM data for scans uploaded to TRIAD are transferred to Rave through Rave Web Services, and populate eCRFs in the patient's record. Validation of this system is outside the scope of SWOG's deliverables.

A summary of the validation and compliance for the TRIAD imaging repository is attached and can be found online at https://triadhelp.acr.org/TRIADOverview.aspx.

CTSU OPEN Patient Enrollment System

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system for the enrollment of patients onto NCI-sponsored Cooperative Group and other select NCI-sponsored clinical trials. This system was developed to leverage the existing Cancer Trials Support Unit (CTSU) Enterprise system for regulatory and roster information and the existing integration of the CTEP Enterprise and Cooperative Group management systems. OPEN uses a multi-tiered distributed application model built on the J2EE platform. It uses the "Spring" open source application framework and the "Hibernate" open source data access framework. SWOG is mandated to use OPEN for enrollment on its NCI-sponsored trials. Validation of this system is outside the scope of SWOG's deliverables.

CTSU's documentation on security, Cancer Trials Support Unit (CTSU) Security Overview, Revision 06 May 6, 2015 (copy attached), provides a brief summary of their compliance on Page 5:

> **Is OPEN 21 CFR Part 11 compliant?**
>
> Yes. CTSU hired a third party to audit OPEN for compliance with the U.S. Food and Drug Administration's (FDA) Code of Federal Regulations, Title 21, Part 11 (21 CFR Part 11) – Electronic Records; Electronic Signatures. It is the criteria under which electronic records and electronic signatures are considered trustworthy, reliable, and legally equivalent to traditional paper records and handwritten signatures. OPEN was found compliant to applicable requirements of 21 CFR Part 11.

Conclusion

This information has been provided to provide insight into data security and compliance related to systems utilized in support of SWOG FDA registration trials that must meet requirements of 21 CFR Part 11.