Clinical Trials Coordinating Center

The UC Davis CTO set up the coordinating center infrastructure in accordance with the best industry trial management practices. Currently it supports an investigator-initiated study in hemophilia with 20 centers across the US (INITIATE, NCT#03204539). The Coordinating Center has experience in enrolling multiple sites in logistically complicated treatment protocols, with focus on rare diseases.

The UC Davis CTO is an integral part of the UC Davis Clinical and Translational Science Center (CTSC), one of the 60 centers across the US, supported by a NCATS Clinical and Translational Science Award. Each component of the CTSA program is crucial in supporting the mission of Accelerating Discoveries Toward Better Health. The UC Davis CTSC is in its third renewal cycle. UC Davis is part of the national SMART Institutional Review Board (IRB) Reliance, Federal Demonstration Partnership (FDP) Agreement, UC System IRB Reliance Agreement, and Trial Innovation Network.

The UC Davis CTO Coordinating Center implemented innovative regulatory management software system (Complion, Inc), which increases regulatory compliance and substantially reduces the cost for quality assurance. Each site in a multicenter network has access to its own regulatory binder and a shared binder, which is a source of the most recent up-to-date regulatory documentation. Audit trails allow Coordination Center staff to track downloads of shared materials. On-demand reports reveal completeness and audit-readiness of site documentation. The Coordinating Center’s Monitor/CRA can access site documentation and deidentified source documents as a part of remote monitoring strategy. This reduces the costs associated with the presence of a CRA/monitor on site and makes feasible implementation of a study with rather limited resources. Complion software provides the required audit trails, eSignatures and access controls. Complion maintains vendor SOPs that are regularly audited by third parties for software development and validation, as well as HIPAA security and privacy. Complion data center is highly secure with documented SOPs for the management of new software installation/validation, backups and disaster recovery. Each Complion instance at UC Davis is validated for each trial in accordance with 21 CFR Part 11. Validation documents will be available for the FDA inspection. UC Davis Coordinating Center will provide thorough training to sites and establish site regulatory management team. All communication with sites will be done through the Complion software ensuring audit trail and consistency of information dissemination. We will amend the license for the software for each trial in the network.

The UC Davis CTO Coordinating Center operates under the Integrated Quality Management Plan (IQMP) that can be easily leveraged to any study managed by the CTO. The set of Quality tools was developed based on the model guidelines for RBM recently established by TransCelerate Biopharma, Inc. IQMP includes, in addition to the component mentioned above, the set of Standard Operating Procedures, Monitoring/CRA templates, DSMB, training matrices and many other foundational quality documents. Risk Assessment Template will be amended to include specific pediatric and neurodevelopmental issues. Risk mitigation strategies will also be amended accordingly, and translate into actionable plans:

1. **Risk Assessment (RACT):** Defines program and/or project level errors (risks) which could affect patient safety, data integrity or regulatory compliance; while considering the impact, likelihood of error (probability) and the extent to which the error would be detectable. Risk assessment is reviewed by cross-functional study team to evaluate Study risks and potential mitigations.
2. **Risk Management Log:** an output of Risk Assessment, a tool that can be used by the cross functional team to track and monitor the progress and actions relating to identified risks. Includes methods and checklists that may prevent errors and decrease risk.
3. **Safety Plan:** Describes how pharmacovigilance/drug safety will manage safety risks related to a product. Includes Medical Monitoring Plan, which describes clinical science/medical monitoring data review and cleaning activities. Includes DSMB Chapter.
4. **Data Management Plan**: Describes the procedures for data collection/review/cleaning. Indicates specific roles and functionalities in data management.
5. **Monitoring Plan**: Describes the remote/offsite and on-site monitoring activities based on the identified risks. Includes risk indicators (triggers) that will help to drive decisions on the type of monitoring to be conducted
6. **Training Plan**: Describes what trial specific training will be provided to all parties involved in the clinical trial, (e.g. study management teams, monitors, investigator sites and vendors. Includes a specific training matrix for all team functions.
7. **Quality Plan**: Describes quality assurance/management activities. Provides tools and materials to ensure compliance to regulatory requirements and inspections

In addition, the CTO is able to leverage a set of Standard Operating Procedures, specifically designed to provide quality assurance to the Coordinating Center Operations, independent of the study being performed:

1. **SOP Organization**
2. **Coordinating Center Training**
3. **Vendor Management**
4. **Clinical Trial Evaluation**
5. **Clinical Trial Risk Management**
6. **Creation of Study Documents**
7. **Management of Study Documentation**
8. **Informed Consent Forms**
9. **Investigator and Site Selection**
10. **Financial Disclosure**
11. **Study Initiation**
12. **Investigative Site Training**
13. **Monitoring Procedures**
14. **Securing Investigator Compliance**
15. **Clinical Test Product Accountability**
16. **Clinical Trial Data Management**
17. **Electronic Data and Signatures**
18. **Reporting Requirements**
19. **Safety Monitoring and Adverse Events**
20. **Complaint Reporting**
21. **Audit Procedures**

We believe that the strong foundation of quality assurance creates an ability to execute any interventional trials with the highest standards of quality.

Another operational innovation comes from utilizing a paperless process for disseminating budget information to sites and just-in-time invoicing of the Coordinating Center by the sites. This substantially reduces errors in financial management and speeds up the payment process. The CTO has implemented financial management and invoicing software (by Merge eClinical, 21 CFR Part 11 Compliant software) that is being utilized in an innovative way, enabling a completely paperless invoicing of the Coordinating Center by the sites. As patients proceed through a clinical trial, the activities are recorded in Merge. Invoicing for the activities in accordance with the negotiated contract is achieved by a single click. This eliminates paper-based invoices, establishes an audit trail and enables just-in-time correlation between activities on the trail and payments for services and procedures. UC Davis is highly experienced in negotiating the budgets with industry sponsors, as well as in creating payment terms and negotiating budgets with the sites. UC Davis Health Clinical Trials Contracts is a team of experienced lawyers dedicated to negotiating the clinical trial agreement. For trials sponsored by the NIH, FDA and other governmental agencies, Federal Demonstration Partnership (FDP) agreement could be used. UC Davis is the part of the FDP consortium. UC Davis CTO provides thorough on boarding and training on the Merge software, as well as manages permissions for the sites. We are highly experienced in generating invoices, collecting payments and achieving financial solvency of the trials.

The UC Davis CTO is experienced in developing comprehensive electronic data capture and establishing validation per 21 CFR11, ICH E6 GCP, and FDA Electronic Data Guidance Documents (Computerized Systems Used in Clinical Trials and Electronic Records; Electronic Signatures - Part 11, Scope and Application). A vendor creates a preliminary draft of electronic case report forms (eCRFs) and overall layouts, reviewed by the Coordinating Center team. The team provides iterative comments, corrections, and feedback to ensure that all data points are captured appropriately. Before the database is released to production, the database design with the data entry screens is validated using test data. The eCRFs are validated in two steps:

1. **Approval of the eCRF Layout.** The eCRF Layout represents the eCRF structure with all visits, eCRF pages and data entry fields. The eCRF Layout is printed as PDF file and is a visual representation of the data entry screens.
2. **Approval of the edit checks (plausibility checks), as specified in the Data Validation Plan.** After the approval of the eCRF layout, the edit checks are implemented, tested and released. In practice, implementation of routine edit-check functionality (e.g. vital signs range checks) will start with generating the eCRF Layout. The validation uses a pass/fail concept of testing and will be documented with details of any test case, actions taken and re-test results. The Coordinating Center Project manager participates in the User Acceptance Test (UAT) of the electronic case report form database (eCRFDB). The eCRFDB release and the date of release to production environment will be documented.
3. **The programmed edit checks are validated within a dedicated test site as part of the study database (eCRFDB) or, if applicable, with copy of the study database on a test server.** Each check shall be validated:
   - with data that shall cause an error message, and
   - with data that shall not cause an error message.
During testing, data in the eCRF that shall cause error messages may be changed. The validation results are captured in the Edit Check Validation document (test report). Edit checks programmed in the database generates automatic system (online) queries in the eCRF immediately after data is entered and saved by the site.

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