FDA Registration Trials

Aisha Shah
CRP Information Meeting, Conducting FDA Registration Trials

November 1, 2018
Goals

- Registration Trial Considerations
- DTL and RCR
- AE Submissions
- Essential Documents
- Protocol Training
- Auditing and Monitoring
- PI Oversight
- FDA Inspection
REGISTRATION TRIAL CONSIDERATIONS
Alliance and NCI Initiatives: IND/NDA Trials

- Initiatives and Process Changes Implementation 2017-2018
- Improve regulatory authority inspection readiness; implement risk-based monitoring approach
  - Centralized Monitoring
  - Audits with TSDV in Rave
  - Centralized Delegation of Tasks Log (DTL)
  - Centralized Registration and Credential Repository (RCR)
- CTEP-AERS/Rave Integration
- Alliance standardized approach to registration trials for all pharmaceutical partners
Delegation of Tasks Log (DTL) – *What is it?*

- NCI to focus on registration trials with central DTL
- Online application by CTSU that is used to define and maintain site personnel listing and their roles/responsibilities
- Via CTEP’s *Registration & Credential Repository (RCR)*
  - Clinical Investigator per protocol
  - Study team per protocol per site
  - Verifies qualifications of study personnel – e.g. ICF, H&P, eligibility, toxicity, data entry, etc
Delegation of Tasks Log (DTL) – Why?

- Ensures that there are no gaps at the site-level per FDA requirements (DTL is complete before enrollment)
- DTL + registration documents from RCR to create Study Site Registration Packet
  - Registration types – Investigator, Non-Physician Investigator, Associate Plus, Associate, Associate Basic
  - Documentation that responsibilities are delegated to qualified personnel
- Protocol-specific training
Delegation of Tasks Log (DTL) – Why?

- Audit – Per CTMB guidelines (August 2017), *The auditor will review the log to evaluate appropriate implementation and maintenance*

- Deficiencies:
  - Critical – any finding identified before or during an audit that is suspected to be fraudulent activity
  - Major – performing tasks not assigned to individual, failure to keep DTL current, individual not listed on DTL, etc
  - Lesser - other
Site staff responsible for conduct of protocol leading submitted study data

Clinical Investigator (CI) – responsible for overseeing the conduct of the protocol at the site. Must have active CTEP registration w/ investigator-type & be on a participating site roster
Delegation of Tasks Log (DTL) – Who?

- Infusion nurses?
- Lab personnel?

- The DTL is designed to capture individuals that significantly contribute to the protocol data at the site in the general task areas outlined on the DTL.
- There is no formal definition of ‘significant contributor’, but guidance provided by the FDA on completion of the Form FDA 1572 can be found at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf
- In general, hospital staff providing ancillary or intermittent routine care are not considered significant contributors.
Registration & Credential Repository (RCR)

- Self-service online registration application for study personnel
  - FDA Form 1572
  - Registration Types require different regulatory documentation – 1572, FDF, NCI Biosketch (education training, certification, license), CV, HSP & GCP training
- Allows access to CTEP applications, e.g. Rave, OPEN, etc
- DTL access for site/protocol maintenance
Adverse Event Submission Requirements for Registration Trials

Shauna Hillman
CRP Information Meeting, Conducting FDA Registration Trials

November 1, 2018
AE Submission Requirements for Registration Trials

- **Changes**
  - Instead of reporting the maximum grade that occurred during the treatment cycle, all changes in grade must be reported.

- **Additions**
  - Verbatim term
  - Start date of the AE
  - End Date of the AE
  - On-going status

- **AE user guide is available on the CTSU website**
  - Covers persistent, intermittent and recurrent AEs

A link to this user guide is available in the help text.
Example of Link to User guide

Link is Available for Cabinet-Trial A021602
### CTSU Website

The image displays the Resources section of the CTSU (Cancer Trials Support Unit) website. It shows a list of resources categorized under different headings such as My Protocols, My Favorites, Experimental Therapeutics Clinical Trials Network (ETCTN) Program, CTSU Operation Information, Sessions, & Events, CTSU Forms, User Guides, Researcher Resources, Educational Multimedia, Site Advisory Panel, Translated Short Form Consents, Disease Portfolios, Protocol Specific Materials, Frequently Asked Questions (FAQs), Glossary and Acronyms.

The Resources section includes a table with columns labeled as **Title**, **Revision Date**, and **Date in Database**. The table highlights specific resources, such as:

1. CTEP Guidance for Recording Adverse Event Start and End Date in Rave
   - Revision Date: 01-Feb-2018
   - Date in Database: 20-Mar-2018
   - Download Format: PDF
   - Availability: No

Other resources mentioned in the table include:

2. Delegation of Tasks Log (DTL) Fact Sheet
   - Revision Date: 01-Dec-2017
   - Date in Database: 21-Dec-2017
   - Download Format: PDF
   - Availability: No

3. DTL Master Task List
   - Revision Date: 16-Mar-2018
   - Date in Database: 22-Mar-2018
   - Download Format: PDF
   - Availability: No

4. Medidata Patient Cloud ePRO Fact Sheet
   - Revision Date: 02-Jun-2017
   - Date in Database: 11-Oct-2017
   - Download Format: PDF
   - Availability: No

5. National Coverage Analysis - CTSU Initiative Slides
   - Revision Date: 20-Apr-2015
   - Date in Database: 10-Aug-2015
   - Download Format: PDF
   - Availability: No

6. Regulatory Submission Portal - Quick Start Guide
   - Revision Date: 14-Dec-2016
   - Date in Database: 14-Dec-2016
   - Download Format: PDF
   - Availability: No

7. CTSU Overview PowerPoint Presentation
   - Revision Date: 15-Jun-2015
   - Date in Database: 16-Jun-2015
   - Download Format: PDF
   - Availability: No

8. CTSU Dashboard Management
   - Revision Date: 06-Jul-2015
   - Date in Database: 07-Aug-2015
   - Download Format: PDF
   - Availability: No

9. CTSU Dashboard - Using Filters
   - Revision Date: 07-Aug-2015
   - Date in Database: 07-Aug-2015
   - Download Format: PDF
   - Availability: No

10. NCTN Per Case Management Funding Information For Sites
    - Revision Date: 21-Sep-2015
    - Date in Database: 22-Sep-2015
    - Download Format: PDF
    - Availability: No

11. Instructions for Getting Started With the CTSU
    - Revision Date: 25-Jul-2015
    - Date in Database: 14-Sep-2017
    - Download Format: PDF
    - Availability: No

12. NCTN Implications for Sites - Slide Set
    - Revision Date: 20-Feb-2014
    - Date in Database: 20-Feb-2014
    - Download Format: PDF
    - Availability: No
Rave – CTEP-AERs Integration

- Purpose: Synchronize routine and expedited Adverse Event (AE) data collection
- Purpose: Provide the site with guidance about whether an AE does/does not need to be submitted as a Serious AE in an expedited fashion
- Required for all trials where CTEP holds the IND starting October 2017
  - Implemented in A031501, A021502, A091605, A021602
Rave - CTEP-AERs Integration

- **Main Changes**
  - The timing of AE reporting
    - AE data must now be *first reported in Rave*
    - All updates to AE data must be first made in Rave, then resubmitted for rule evaluation
  - All AEs ≥ grade 0 must be sent for rule evaluation
Rave - CTEP-AERs Integration

- Both solicited and “other” AEs are reported on the same form.
- The report period end date should only be recorded when the cycle is complete as this drives querying.
- An Expedited Reporting Evaluation Form must be submitted to send all AEs recorded on the AE form for rule evaluation to determine if any need to be reported in an expedited fashion via CTEP-AERs.
Tips for AE Form Submission

All fields required for rule evaluation are identified with a red asterisk.

The site should leave report period end date missing until after completion of the entire cycle and form.
Do not respond to query, it will go away automatically when the report period end date is added. Please leave as a reminder that the form is not complete.
This field is derived from the AE form for cycle 1, if missing enter on the cycle 1 AE form.
## Tips for AE Form Submission

**AE evaluated is defaulted to “Pending” and must be updated when AE is evaluated.**

**AE start/stop dates and ongoing status are new, ongoing status is derived based on presence of AE stop date.**

**After AE is submitted for rule evaluation the AE specific recommendation can be found here.**

### Verbatim term is new

- Indicator of whether AE is solicited

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**REMINDER:** Depending on your settings in Revit, this table may be paginated. If the options are available, click on 'Paginate' and select 'Show All Lines' or click on the numeric page numbers at the bottom right corner of the table. If these options are not available, you are already viewing the entire table.

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<th>Verbatim term</th>
<th>AE evaluated this cycle?</th>
<th>AE grade description (first 120 characters)</th>
<th>AE start date</th>
<th>AE end date</th>
<th>AE ongoing</th>
<th>Attribution to study intervention (grade &gt; 0)</th>
<th>None</th>
<th>Hospitalization</th>
<th>Life-threatening</th>
<th>Death</th>
<th>Disability</th>
<th>Congenital anomaly/birth defect</th>
<th>Required intervention</th>
<th>Other</th>
<th>SAE report recommended (derived)</th>
<th>AE entry date (derived)</th>
<th>*Time zone (derived)</th>
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<table>
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<th>Verbatim term</th>
<th>AE evaluated this cycle?</th>
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<th>AE entry date (derived)</th>
<th>*Time zone (derived)</th>
<th>AE event term (CTCAE v4.0) (Derived)</th>
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<td>Fever</td>
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<td>Fever</td>
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</tbody>
</table>
A query fires anytime a new AE is entered or an existing AE is updated. Check the checkbox and save the form to submit the AE for rule evaluation.

If a query is present on the AE form, you will NOT be able to send the AE for rule evaluation until after the query is resolved, exception is the query that fires on the report period end date.

Recommendation provided here and is populated after form is submitted, if the site disagrees they may override.

Link to CTEP-AERs here.
Rave – CTEP–AERs Integration

- All Alliance trials must use the new AE Form
  - verbatim term, AE start date, AE end date and ongoing status fields required for Registration trials only
- All changes in AE grades must also be captured for Registration trials only
- Integration required for all trials where CTEP holds the IND
Rave – CTEP–AERs Integration: Misc Notes

- The sticky notes found on the Expedited Reporting Evaluation Form are for instructional purposes only and there is no way to remove them from your Rave Task Summary.

![Recommended action for report (derived)](image)

- An expedited report is NOT recommended. If the Investigator believes an expedited report is warranted, use the link below to move to CTEP-AERS to complete the expedited report.[QC019]
  Opened To Site from System (15 Aug 2018)
  
- Click this link to complete the safety report

- The AE Start Date cannot be before the start date of cycle 1, if a pre-existing condition, enter the start date of cycle 1.
Rave – CTEP–AERs Integration: Misc Notes

- You do not have to wait until all solicited AEs are evaluated to run the rule evaluation, the form is designed for you to evaluate AEs in real time
- If all AEs are reported, you do not have to submit each AE for rule evaluation, saving the Expedited Reporting Evaluation Form will result in all AEs on the AE form being evaluated.
Any Questions?
Essential Documents at Sites (*ICH E6, Section 8*) –

1. Investigator Brochures
2. Protocol and amendments
3. ICF (and any other study info distributed to patient)
4. Subject recruitment info
5. IRB/Independent Ethics Committee
6. Investigator CVs
7. Lab certification/accreditation
8. IP - handling instructions & shipping records & DARF
Essential Documents at Sites (ICH E6, Section 8):

1. Monitoring letters
2. Correspondences b/w IRB & Institution
3. AE/SAE/SUSAR/UPIRSO – site-specific SOPs, if applicable
4. Protocol-specific training
5. Screening/enrollment logs, per site SOP
Essential Documents – Don’t Forget:

- Sites should also have copies maintained of:
  1. RCR – 1572, CV, License, FDF
  2. DTL
  3. Regulatory Support System (RSS) – regulatory approval, protocol amendments, continuing renewal, site termination letter from IRB, protocol-specific-training, +/- ICF templates
  4. COI Disclosure Form
## Protocol Review Log

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The individuals listed below have reviewed the protocol with the PI or designee and understand their roles and responsibilities.

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<th>Name (Please Print or Type)</th>
<th>Role</th>
<th>Signature</th>
<th>Date</th>
<th>PI/Designee Signature</th>
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</tbody>
</table>
Protocol Training

- Importance of maintaining log?
  - Protocol amendments
  - Staffing changes at the site
- FDA-inspection readiness
- Do you know your site’s SOP?
  - Alternative/Back-up documentation
- Webinars for Alliance registration trials posted to Alliance website
  - Study-specific page -> supplemental materials
Auditing & Monitoring

- Monitoring
  - Overseeing progress of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and regulatory requirements

- Auditing
  - Systematic & independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor’s SOPs, GCP, and regulatory requirements
Monitoring

- Mandatory per federal regulations (21 CFR812.3 (j), 812.25, 812.40, and 312.50)
- During a US regulatory audit, FDA has access to monitoring reports and their associated action items
  - Importance of addressing action items on a monitoring letter/report in a timely fashion
Monitoring

- Depending on the study-specific monitoring plan, the following is routinely monitored:
  - Informed consent Documents
  - Eligibility criteria
  - Protocol compliance
  - Source data verification for data accuracy
  - Query resolution
  - AEs – occurrence and reporting
  - IP accountability
  - Essential documents
  - Clinical Investigator (CI) & IRB oversight

- CI is adequately informed of responsibilities to recruit eligible subjects & collect high quality data
Central Monitoring to Support Registration Trials

Shauna Hillman
CRP Information Meeting, Conducting FDA Registration Trials

November 1, 2018
Alliance Central Monitors

- Tiffany Schafer

- Sara Goodman
Central Monitoring

- **Introduction**
  - Central Monitoring (CM) is performed by Lead Protocol Organizations (LPOs) to ensure protocol compliance by sites
  - It consists of remote review of source documents against data entered in Rave
  - The Source Document Portal (SDP) is an application on the CTSU website in the Auditing & Monitoring tab used to support the collection of source documents for CM review
Central Monitoring-Current Status

- The CTSU SDP is not in use for any current Alliance trials
- Central Monitoring (CM) is being conducted for the following trials
  - A031501-Ambassador
  - A021502-Atomic
  - A021602-Cabinet
  - A041701-Future trial
- CM is currently being facilitated by uploading source documents on the Source Document Form within Rave
Example of Baseline Source Document Form for Atomic Trial

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<tr>
<th>#</th>
<th>Serial # of document</th>
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Source Document Reminders

- Redact all source documents before uploading.
- The Informed Consent Document should include all indications to the optional correlative studies.
- When ‘yes’ is provided for the disease assessment question, you must provide source documentation (imaging, biopsy, etc.).
Source Document Reminders

- Source documents required for treatment may not be required for every cycle of treatment
- Current requirements for Atomic

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<th>Treatment (Intervention)</th>
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</tr>
<tr>
<td></td>
<td>Dose delay reason</td>
</tr>
</tbody>
</table>
Where to Find the Needed Source Documents

- Data Submission Schedule for A021502 & A021602, protocol for A031501
Data Submission Schedule SD
Requirements for Monitoring

SOURCE DOCUMENTATION REQUIREMENTS FOR MONITORING
The following data and documents will be reviewed through central/on-site data monitoring and source data verification (SDV) activities.

<table>
<thead>
<tr>
<th>Domain</th>
<th>CRF</th>
<th>Data Fields/Section</th>
<th>Acceptable Source Document</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>Informed Consent 1</td>
<td>Date of signature^1</td>
<td>Informed Consent Document</td>
</tr>
<tr>
<td></td>
<td>Informed Consent 2</td>
<td>Signature page^1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entire document</td>
<td></td>
</tr>
</tbody>
</table>

Source Document: Need a source document that will validate the data entered in the given CRF - data field.
Future Initiatives

- Alliance is in the process of selecting a future trial to implement the CTSU SDP
- There are no plans to implement the SDP for trials that are already activated
- Alliance is working out how to use the SDP to facilitate both source documents needed for central monitoring and source documents needed for eligibility reviews and case evaluations
Any Questions?
Auditing

- Quality assurance function
- Auditors can assess a wider study sample than monitors and can help evaluate trends at various levels
  - single or multiple sites and/or multiple studies
  - trial vendors/sponsors
- Evaluate compliance to recognized standards
  - FDA’s Code of Regulations
  - International Conference on Harmonization
  - International Standards Organization
  - SOPs
Auditing

- Compliance snapshot
- Can assist in determining effectiveness of:
  - Monitoring
    - Importance of addressing action items on monitoring reports in a timely fashion
  - Study team
- Manage non-compliant sites
- Assess inspection readiness
Investigator Oversight

- How often do you meet with your investigator?
- Are routine meetings established?
- Process for obtaining signatures/assessments?
Investigator Oversight – *How to demonstrate?*

- Timely signatures on source documents
  - Diagnostic procedures –
    - Recist reads
  - Lab results
  - Eligibility criteria
  - Treatment authorization
- DTL – appropriate and qualified staff delegation
- SAE/SUSARs - evaluated and submitted in a timely manner
Investigator Oversight – *How to demonstrate?*

- Feedback from the FDA suggests they are concerned with one Clinical Investigator covering multiple sites and protocols.
  - No hard rule as to how many sites/protocols a CI may cover.
  - May be a reason for triggering an audit.
FDA Inspection Readiness

- On-going state of effectiveness and suitability monitored through periodic review and monitoring of compliance
  - Not a preparation activity
  - Requires Investigators and management to be actively involved and committed to culture of compliance

- FDA Bioresearch Monitoring (BIMO) Inspection Program
  - Protects the rights, safety, and welfare of human research subjects
  - Assures quality, reliability, and integrity of data collected
FDA Inspection Focus at Sites:

- CI oversight
- Site management
- Data
- Investigational product (IP) management
- Adverse Events
FDA Inspection Process:

1. Notification of inspection via FDA Form 482
2. Opening meeting
3. Interview of site staff
4. Review of study-related/source documents
5. Exit meeting
   - Review findings
   - Address issues or concerns
6. Response to inspection, as needed
FDA Inspection – What to do if issued FDA Form 482?

- Alliance and/or pharmaceutical partner will:
  - Provide additional instructions & guidance for preparing
  - Provide a single point of contact (SPoC) at Alliance for any issues that may arise during the inspection
  - Site should also provide daily report to Alliance SPoC
  - SPoC will assist in preparing responses to the inspection findings, if needed
FDA Inspection – Role of Investigator/Site

- Ensure availability of staff during inspection
  - Alert other staff of section, so that they know to avoid lingering in areas hosting the inspection & to watch conversations near inspectors
- Ensure availability of study-related records & provide copies to HA as requested
- Answer questions regarding your role
- At the end of each day, request a summary from the inspector
  - Forward summary to Alliance SPoC
- Respond to any inspection findings, as needed
FDA Inspection – **Role of Alliance**

- Assign SPoC to site
- Provide daily status report to pharmaceutical partners
- Provide ongoing support to site/investigator before, during, and after
FDA Inspection – *Tips for Interacting with Inspectors*

- When answering questions:
  - Honestly
  - Be concise & clear – only answer the question asked
  - Don’t argue with inspector
  - Don’t answer hypothetical questions
  - Wait until you have heard & understood the whole question

Beware of pauses – don’t feel like you need to keep talking
FDA Inspection – *Findings*:

- Criticality determined by deficiencies that:
  - Affects rights, safety, or welfare of subjects
  - Impacts data integrity
  - Indicates systematic problems within the study from the Sponsor
  - Indicates problems with the investigator/site that may impact other studies
- FDA Form 483, *Inspectional Observations*, documents & communicates concerns discovered during inspections

Forward to Alliance SPoC, immediately!
FDA Inspection – **Resources:**

- FDA regulatory info for clinical trials: https://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm
- FDA Cooperative Research Information Sheet: https://www.fda.gov/RegulatoryInformation/Guidances/ucm126422.htm
- FDA Bioresearch Monitoring Info: https://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm
Any Questions?