Streamline the Document Collection Process: Efficiently Capture the Right Info from the Right Source

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The Cleveland Clinic Experience

Heart and Vascular Institute

Department of Cardiovascular Medicine
Chairman: Steven E. Nissen, MD

C5Research
Medical Director: A. Michael Lincoff, MD

Clinical Events Committee (CEC)
Medical Director, Venu Menon, MD
C5Research

- Cleveland Clinic Coordinating Center for Clinical Research
- Academic Research Organization founded in 1991
- Provides
  - Project Development
  - Project and Site Management
  - Biostatistical support
  - Core labs e.g. CEC, IVUS, Angio, Echo, CIMT

http://c5research.clevelandclinic.org
Cleveland Clinic CEC Experience

• Metrics for 2014
  – 10,959 endpoints adjudicated
  – 85% CV, 10% Neuro, 5% GI / Renal
  – 54 Active Committee Members
  – 22 Drug Studies and 4 Medical Device Studies
Cleveland Clinic CEC Experience

Event Types

- Death
- MI/HUA
- TIA/Stroke
- Heart Failure Hospitalization/Event
- Percutaneous Coronary Intervention
- Peripheral Vascular Intervention
- Pancreatitis
- GI Events (Bleeding/Obstruction)
- Fracture Events
- Rash Events
- Serious Arrhythmia
- Valve Deterioration/Re-intervention
- Endocarditis
CEC- Flow Process

Endpoint Suspected
Investigator-identified or triggered by prespecified criteria

Package (CRF, source documentation) reviewed by CEC project manager

Additional source documents requested if necessary

Phase I physician adjudication

Manual review by CEC project manager

Agree

Disagree

Additional source documents requested if necessary

Phase 2 physician adjudication

Complete
Major Steps in the Adjudication Process

• Identification of End Points
  - Primary: Site Investigator reporting
  - Secondary: Triggering process (MedRA)
  - Secondary: Ad hoc (CEC, Monitors, Safety)

• Collection of supporting documentation for each endpoint

• Adjudication of the event
Source Data

• “All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).”

ICH E6 1.51
Source Documents: Purpose

“To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subjects.”

ICH E6 8.3.13
Source Documents: Definition

• Original documents (certified copies), data, and records
• Examples
  - Hospital Records
  - Clinical and office charts
  - Labs reports
  - Pharmacy records etc.

ICH E6 GCP Glossary 1.5.2
Source Documents: Informed Consent

Who has access: monitor, auditor, IRB, regulatory authorities

To what: original medical record

Purpose: verification of clinical trial procedures and/or data

ICH E6 4.8.10 (n)
Source Documents: eCRF / CRF

• CRF data: supplementary/secondary to source data

• Issues with using CRF data for Adjudication
  - CRF data changes
  - CRF often not clean until the end of the trial

2013 FDA Guidance: Electronic Source Data in Clinical Investigations
2010 EMA Reflection Paper on Expectations for Electronic Source Data.
What Documentation to Collect?

• Begin with the **endpoint definitions** utilizing
  - recognized standards* / classifications
  - clinical experts

• Decide what **elements of the patient’s record** will support the criteria.

• Understand **where the documentation may be located**.

Source Document Collection Tool

Required Documents Checklist

Should serve as a **guideline**

It is important to distinguish “not done” versus “not available”

<table>
<thead>
<tr>
<th>Documents</th>
<th>Sent</th>
<th>Done but not available</th>
<th>Does not apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>Date</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>Date</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Hospitalization for Unstable Angina</td>
<td>Date</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Summary of Hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission, Emergency Room, first responder, and clinic visit notes</td>
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<tr>
<td>All 12 lead EKGs (plus a baseline done anytime prior to the event)*</td>
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<tr>
<td>All CK, CKMB &amp; troponin lab values AND normal range*</td>
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<tr>
<td>Coronary Angiography Report</td>
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<tr>
<td>Coronary Revascularization Report (surgical or peripheral)</td>
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<tr>
<td>Diagnostic Tests (i.e. echocardiograms, stress tests, etc)</td>
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<td>Cardiology Consult Records</td>
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<tr>
<td>Other</td>
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<tr>
<td>Peripheral Revascularization Procedure</td>
<td>Date</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Peripheral Arterial Event</td>
<td>Date</td>
<td>/</td>
<td>/</td>
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<tr>
<td>Summary of Hospitalization</td>
<td></td>
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<tr>
<td>Physical Exam Findings including time/date of symptom onset &amp; resolution</td>
<td></td>
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<tr>
<td>Peripheral Angiography Report</td>
<td></td>
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<tr>
<td>Peripheral Revascularization Report (surgical or peripheral)</td>
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<tr>
<td>Doppler and Duplex Ultrasound Report(s)</td>
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<tr>
<td>CAT and MRI report(s)</td>
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<tr>
<td>Laboratory Values AND normal range*</td>
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<tr>
<td>Medication Reports (including thrombolytics)**</td>
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<td>OI</td>
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Source Documentation: Adjudication Form

- **Sufficient**

- **Insufficient**
  - All necessary assessments not performed
  - Assessments most likely performed but not available
  - Unclear if assessments performed
  - Source not available
Source Documentation: Narrative

• What is a narrative
• What does it include
• When do you use a narrative
• What format do you use
Sample Events with Definition and SD

• Death
• Myocardial Infarction
• Stroke/TIA
• Heart Failure
Death: Classification

Death is classified into 1 of 3 categories

• Cardiovascular death
• Noncardiovascular death
• Undetermined cause of death

“Collection of appropriate source documentation is critical for rigorous adjudication of the cause of death.” *
Death: Source Documentation (SD)

- Verifying date and cause
- Death certificate
- Autopsy report
- Admission notes, ER/CDU reports, first responder notes, witness notes, discharge summary, consults, procedural reports.
- Laboratory values and normal ranges (biomarkers)
- 12 lead ECGs (all, and baseline ECG).
Myocardial Infarction: Definition

• Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least 1 value >99th percentile of the URL and at least

• At least 1 of the following:
  - Symptoms
  - ECG changes
  - Imaging
  - Evidence of intracoronary thrombosis
Myocardial Infarction: Source

- Biomarkers Lab reports
- At least 1 of the following:
  - Symptoms Clinical notes
  - ECG changes All including baseline
  - Imaging Reports and Digital Images
  - Evidence of intracoronary thrombosis
    Angio/autopsy reports, PCI surgery notes

*Same source for UA Hospitalization, Coronary Revasc
Stroke/TIA: Definition

**Stroke:** An acute episode of focal or global neurological dysfunction, caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

**Diagnosed by**
- imaging or
- persistence of symptoms

**TIA:** Transient episode of focal neurological dysfunction caused by...without infarction.
Stroke/TIA: Source Documents

**Stroke**: An acute episode of focal or global neurological dysfunction, caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction

Diagnosed by

- imaging or Imaging reports

- persistence of symptoms ER/Admission notes, consult notes

**TIA**: Transient episode of focal neurological dysfunction caused by....without infarction.
Heart Failure Event: Definition

- Event: Presentation for an urgent, unscheduled clinic/office/ED visit or hospitalization
- New or worsening symptoms
- Objective evidence at least
  - 2 physical exam findings OR
  - 1 physical exam finding and at least 1 lab criteria
- Receives initiation or intensification of treatment
Heart Failure: Source Documents

- An urgent, unscheduled clinic/office/ED visit or hospitalization. New or worsening symptoms Physical exam notes, X-ray, echo,

- Objective evidence at least
  - 2 physical exam findings OR
  - 1 physical exam finding and at least 1 lab criteria

- Receives initiation or intensification of treatment Medication Records including route
Case Presentation: Clinical picture

- A 52 year old female diabetic, smoker, Hx CAD, enrolled in a CV safety study with a new diabetic agent

- Dx with breast cancer earlier in the year, with radical mastectomy and chemotherapy

- 2 weeks prior developed cough and SOB

- Presenting now with ↑ SOB, fatigue, Hb 9, CR 1.8, pedal edema, chest x-ray venous congestion, patchy atelectasis, left pleural effusion

- Troponin 0.04 ng/ml and 0.06 8 hours apart

- ECG new non specific ST/T wave changes

- Tx’d with IV Lasix, PRBC, antibiotics for presumed bronchitis

STREAMLINE THE DOCUMENT COLLECTION PROCESS | May 5, 2015 |
Case Presentation: Adjudication

- **Cardiologist:** This is a heart failure event. The patient had SOB, fatigue, pedal edema and CXR suggests some congestion. She was placed on IV diuretics. The troponin reflects heart failure likely due to injury from chemotherapy. Echo and BNP would be helpful.

- **ED physician:** This is a type 2 myocardial infarction. The patient has established CAD, positive troponin, minor EKG changes with symptoms of new SOB in the setting of anemia. Imaging and angiogram would be helpful.

- **Internist:** This is a no event. Her symptoms are best explained by a bronchitis and anemia. Her edema is likely related to her new diabetic agent / ↓ albumin.
The Blind Men and the Elephant
John Godfrey Saxe (1816-1887)

It was six men of Indostan to learning much inclined, 
Who went to see the Elephant (Though all of them were blind), 
That each by observation…might satisfy his mind.
Challenges with Documentation Collection*

- Unclear what “isn’t available” vs. “isn’t easily available”
- Difficulty getting records from another provider (Sites do not budget/plan for the time that this requires)
- International differences in records retention (e.g. documents to the patient, different privacy laws)
- Translation causes delays and at times loss of info
- All ECGs are present, both baseline and event ECGs
Challenges with Documentation Collection

- Obtaining URL vs. ULN for biomarkers
- Obtaining all sequential biomarker /ECG results
- Documentation that includes duration of symptoms
- If the source is the CRF
  - delays from CRF cleaning (improved with eCRF)
  - batching of labs, response to queries
Potential Solutions to Challenges*

• Engage the Primary Investigator

• Persons collecting records should have clinical experience or be well trained

• Site personnel should instruct the subjects on importance of reporting events and allowing access to records. (Release of information forms)

• Definitions should be internationally recognized
Potential Solutions to Challenges

• Source collection process should be included in the site budget

• Create source document checklists

• Consider the benefits of using an electronic adjudication system to accelerate data collection, review and final adjudication.
Adjudication is limited by the events you report and the documents that you provide us.

Thank you in advance for accurately reporting events and collecting all required documents.