Clinical Events Committee
ADJUDICATION EFFICIENCIES

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Goals of Workshop

- When is adjudication necessary
- Scope of Work
  - When to consider using an EAS
- Charter considerations
  - Selecting adjudicators
  - Pros & cons of various processes
  - Endpoint definitions
  - Source document requirements
  - Adjudication Form content
- Site training manuals
- Adjudicator training manuals
- Escalation plans/timelines
- EAS demonstration
When is Adjudication Necessary

- Endpoint is subjective
- Definition is complex
- Intervention being tested is unblinded
- Potential for regional variation
- Investigators are not experienced researchers or specialists in the endpoint area
- Monitoring is limited
- Regulatory Authority requires it
When is Adjudication Necessary

Advantages
- Unbiased
- Reduces variability
- Ease of quality control
- Identify missed events
- Regulatory authorities will not require if AFTER data is submitted

Disadvantages
- Cost
  - Collection of Source Documents
  - Translations
  - Additional database considerations
- Complexity
  - Additional database considerations
  - SAE reporting considerations
Scope of Work and Key Budget Considerations

- Who is going to do what (ARO vs. CRO vs Sponsor)
- **Number of Events**/Event Types and other items to be adjudicated
- Adjudicator Qualifications and Number of Adjudicators
- Workflow (paper vs **electronic** vs hybrid)
- Number of Sites: Source Collection and **Translations**
- Develop Charter, Forms, Training Manuals, etc
- Database/Report development
- **Trigger Programming** and review
- **Database oversight** and UAT
- Meeting attendance
- Payments/contracts
- Regulatory document management
- SOPs/Work Instructions
- Training (site and adjudicators)
- Timelines
Scope of Work - When to Use Electronic Adjudication System

- Duration of trial is long
- Large number of events expected to be adjudicated
- Multiple Adjudicators
- Adjudicators in multiple locations
- Adjudication Process amenable to the EA system
SOW-When to Use EAS

Advantages
- Efficiencies
  - Redacting
  - Paperless-Dossier Creation
  - No shipping/faxing
  - Communication resides in one location (Translations)
  - Shortened timelines
  - FDA submission ease
  - Long term storage

Disadvantages
- Longer start up time
- Up Front Cost
- Complex
### SOW: Who is Responsible for What

<table>
<thead>
<tr>
<th>Description of Service:</th>
<th>CEC</th>
<th>CRO</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of protocol, development of Charter, creation of CEC form content</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Database development/management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjudicator contracts/payments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site/CRA training (per US/OUS investigator meeting) including site manual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEC personnel /Adjudicator training including Work Instructions and Adjudicator Manual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Write Narratives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Communications/minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case Adjudication: Receipt, tracking, adjudication, comparison, entry of final determination into eCRF, QA process (per case)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trigger Program (write/program)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manage Event Identification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect Source from Sites/Site communication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (define): Translations, Shipping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Program Reports</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What is the Magic Number?
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Overview

- **High Level:** Do not confuse this with other process specific documents (training manuals, work instructions, QA plans, etc)
- Goal of the Committee
- Committee’s Scope of Work
- Event Identification
- Adjudicator Qualifications
- Site/CRO/ARO Responsibilities
- Committee Responsibilities

Overview of Process-Workflow
- Timelines
- QA
- Appendices
  - Definitions
  - Source Recommendations
  - Forms
  - References
Adjudication Committee Charter

- Goal of the Committee
- Committee’s Scope of Work
  - Events to be adjudicated
  - Time period for adjudication
- Event Identification Process
  - Investigator Reported
  - MedDRA terms
  - Other
- Adjudicator Qualifications
Charter-Adjudicator Qualifications
Non Celebrity Adjudicators

PROS
- Uniform application of definitions - follows the "rules" rather than (variable) professional experience
- More responsive to requests and timelines
- Less conflicts with schedules and clinical commitments

CONS
- Perceived lack of "experience"
- True lack of experience
Charter-Adjudicator Qualifications

Advantage of pool of experienced adjudicators

- Contracts and CDA in place
- Available for consulting early in trial
- Experienced with adjudication conventions
- Experienced with frequently used definitions
- Familiarity with EAS and Form completion
Adjudication Committee Charter

- Site Responsibilities
  - Identify and Report Events
  - Collect and Redact Source Documents

- CRO Responsibilities
  - Provide EA System
  - Track Reported Events
  - Identify Unreported Events (via MedDRA listings)
  - Collect/Packaged Dossiers
  - Coordinate Translations
  - Correspond with sites
Adjudication Committee Charter

- **ARO Responsibilities**
  - Review submitted packages (academic perspective)
  - Identify unreported events
  - Assign adjudicators
  - Correspond with CRO

- **Committee Responsibilities**
  - Review dossier
  - Make final determination /complete CRF
  - Identify unreported events
  - Correspond with ARO
Adjudication Committee Charter - Work Flow

Endpoint Suspected
Investigator-identified or triggered by prespecified criteria

Source Documents Uploaded to EAS &
reviewed by CRO and then CEC PM

Additional source documents
requested if necessary

2 Independent physician adjudication

Forms/Comments reviewed by CEC PM

Agree

Disagree

Additional source documents
requested if necessary

Phase 2 physician adjudication

Complete
Adjudication Committee Charter
Workflow: Independent Reviews vs. Committee

**Independent**

- **Pros**
  - Rapid Turnaround (no meetings)
  - Avoids excessive influence of one or more particularly vocal reviewers on consensus decision
  - Avoids “hurrying”
  - Avoids batching
  - Forces immediate collection of source documents

- **Cons**
  - Lose the discussion
  - Complicates the “workflow”
  - Must have a “tie breaker” process

**Committee**

- **Pros**
  - Simplifies the “workflow”
  - Allows for “batching”
  - Allows discussion

- **Cons**
  - Slows the turn around time
  - Must schedule meetings around schedules and time zones
  - May have excessive influence of a single adjudicator
  - May hurry to complete
  - Source collection may be delayed and eventually become impossible to get
Adjudication Committee Charter

Workflow: Other options

- Single adjudicator
- Event specific plans
  - Event Type A - single adjudicator (celebrity)
  - Event Type A - single adjudicator (nurse)
  - Event Type B - two adjudicators with a single tie breaker
- Hybrid
  - Independent Reviews
  - Committee for tie breakers
Adjudication Committee Charter

Timelines

- What does the Sponsor want
- What does the Executive Committee want
- What does the Safety Monitoring Committee want
- What do the Regulatory Authorities want
- What is possible?
  - Consider sites have to get source from non-investigative sites
  - Translations
  - Adjudicator schedules/vacations
- Reference the “escalation plan”
Adjudication Committee Charter
QA Plan

- As it relates to the committee
- Reference the separate plan
- Otherwise keep QA separate from other activities
Adjudication Committee Charter

Definitions

- Review the literature
- Regulatory Authorities may dictate
- Adjudicator input
- Define almost every word
- Ensure terminology is aligned with protocol terminology
- Cannot be too vague
- Cannot be too prescriptive
  - Data may not be uniformly available
  - Events may occur in or out of a medical setting
  - Regional or institutional differences in practice patterns
Adjudication Committee Charter

Definitions

- Kappetein AP. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2
- Scirica BM. Supplementary Appendix. Saxagliptin and CV outcomes in patients with Type 2 DM. NEJM 2013.
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.

Ischemic
An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.
Note: Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic
An acute episode of focal or global cerebral or spinal dysfunction caused by intra-parenchymal, intra-ventricular, or subarachnoid hemorrhage.
Note: Subdural hematomas are intracranial hemorrhagic events and NOT strokes.

Undetermined
An acute episode of focal or global neurologic dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

Stroke Terminology Concept

*Stroke/TIA Date-Time*
Date and time of the onset of a stroke/TIA.
Adjudication Committee Charter
Source Document Requirements

**Source Documents**
- Not legible
- Availability of complete records
  - Privacy laws
  - International differences in record retention
  - Unclear what “isn’t available” vs. “isn’t easily available”
- Requires translation
  - Costs
  - Delays
  - Loss of information
- Adjudicators identify events not reported by sites

**CRF Data**
- Legible/No translations
- More CRF programming
- More site entry/monitoring
- Relay on coordinator interpretation of information
- Under reporting of events
- Delay in adjudication
  - Data changes until end of trial
  - Batching of central labs
  - Multiple re-reviews
<table>
<thead>
<tr>
<th>Source Document Type</th>
<th>Document or Narrative Submitted? (Y/N)</th>
<th>Not Done (X)</th>
<th>If anticipated, provide estimated date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission History, Physical Exam, ER report, Discharge Summary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy report (if available)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witness description of death (if no hospitalization records)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death certificate (only if NO OTHER documentation is available)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 lead ECG’s (all, including screening or randomization)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory values and normal ranges</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If MI or Stroke events see below for additional documents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-fatal or Fatal Acute Myocardial Infarction</strong></td>
<td>Date of Event <em><strong>/</strong></em>/20__</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission Notes, ER report, Discharge Summary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiology consult reports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 lead ECG’s (all, including screening or randomization)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All CK-MB, Troponin I or T, and CK with normal ranges</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure reports (catheterization and revascularization)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic reports (stress test, echocardiograms, CT, imaging)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Source Request Algorithm
STROKE/TIA

Always Required

1. Reports of cranial computed tomography (head CT) and MRI (if done)*
2. Neurologist Consult (if done)*
3. Description of onset and duration of neurologic symptoms and physical exam findings at time of symptom presentation to healthcare provider

If not done, provide documentation that these were not performed.
Adjudication Committee Charter

Forms

Contents

- Identifiers (site/subject/UID)
- Event to be adjudicated
- Keep it Simple
  - Event yes/no
  - No more than 1-2 subcategories
  - Date of event
  - Comment field
  - Source quality

Also Consider

- Ensure Terminology aligned with protocol/charter and site CRF
- Ensure statistician reviews
- Ensure safety monitoring is aligned
- Tracking and work flow forms
- How data will be reconciled
  - Site trigger forms
  - Site EP forms
  - AE/SAE forms
Death Adjudication Form

**Primary Cause of Death:** (Check **ONLY** One: Cardiovascular, Non-Cardiovascular, or Undetermined Cause of Death)

**Adjudicated Death Date:** Click here to enter a date.

**Primary Cause of Death** (check **only** one)

- **Cardiovascular**
  
- **Non-Cardiovascular**
  
- **Undetermined Cause of Death** *(Clarify if this should be under CV/NON CV or its own category)*

**Comments:**

________________________________________

________________________________________
Non-Fatal Stroke Adjudication Form

CEC Assessment: (Check ONLY One)

- Yes: If “YES” is checked, please respond to the following:
  - Stroke Date: Click here to enter a date.
  - Stroke Type: (Check ONLY One)
    - Choose an item.

- No

- Insufficient Documentation for Event Determination (Phase I only)

Comments:

__________________________________________________________

Source Quality (Check only one)

- Sufficient to make determination
- Insufficient to make determination (best assessment made)

Choose an item.
Adjudication Committee Charter

References

- Reference the definitions if they are pulled from another publication
- Reference the contributors if they are not pulled from publication
What is an Electronic Adjudication System

- Site Data
- Coordinator Review (CRO)
- Document Review (ARO)
- Phase 1 Adjudication
- Phase 2 Adjudication
- Phase 3 Adjudication
- Outcome

- Event Details
- Source Documents
- Inventory and Review Documents
- Create Dossier
- Review Documents
- Assign Adjudicators
- Multiple Adjudicators
- Parallel or Paired Consensus
- Additional Adjudicators
- OR Committee
- Optional
- Concordance
- Notification
4.0 Process for Capturing Potential Events for Adjudication

Potential Events for Adjudication eCRF Page

At each site visit, the Investigative site will be required to complete the “Potential Events for Adjudication Page” eCRF.

- If the site responds yes to any of the leading questions, they must complete the corresponding Adverse Event eCRF and reference the AE/SAE number on the eCRF.
  - It will be the responsibility of the Safety Specialist to reconcile the data captured on this eCRF and the data captured on the AE eCRF.

Standard MedDRA Queries

MedDRA Queries (SMQ) will be utilized to ensure that all potential MACE events are captured. The following SMQs will be utilized to ensure that events of interest are identified and processed as applicable:

- Cardiac arrhythmias (SMQ)
- Cardiac failure (SMQ)
- Cardiomyopathy (SMQ)
- Cerebrovascular disorders (SMQ)
<table>
<thead>
<tr>
<th>Study</th>
<th>Event Type to be Adj</th>
<th>MedDRA Preferred Term (PT)</th>
<th>Notable LLTs</th>
<th>Adjudicate?</th>
<th>Query?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cardiovascular symptom</td>
<td></td>
<td>Only if hospitalized</td>
<td>Query to update term with location or update with diagnosis (first review other events for a diagnosis and to check to see if another event was sent for adjudication for the same occurrence)</td>
</tr>
<tr>
<td>Cardiac Ischemic Event</td>
<td></td>
<td>Anginal equivalent</td>
<td></td>
<td>Only if hospitalized</td>
<td>Query to update term with location or update with diagnosis (first review other events for a diagnosis and to check to see if another event was sent for adjudication for the same occurrence)</td>
</tr>
<tr>
<td>Cardiac Ischemic Event</td>
<td></td>
<td>Chest discomfort</td>
<td>Chest heaviness, Chest fullness, Chest pressure, Chest tightness</td>
<td>Only if hospitalized</td>
<td>Query to update term with location or update with diagnosis (first review other events for a diagnosis and to check to see if another event was sent for adjudication for the same occurrence)</td>
</tr>
</tbody>
</table>
Demo - Uploading Events from CRF
Site Training Manual

- Purpose
- Contact Numbers!
- Questions
  - Definitions
  - Document Submission
- Site Responsibilities
  - Reporting (reference)
  - CRF Guidelines (reference)
- Source Document Requirements
  - Redacting
  - Tips on obtaining the source
  - Use of Narratives
- Submission of Documents (Electronic will need to be trained on the system)
  - This should be step by step with screen shots (if electronic)
  - Back up process
- Requests for Additional Documents
Demo - Site Upload/Redact
Work Instructions provide the "how to" detail for staff responsible for each step of the Adjudication Process. They should be of sufficient detail such that a co-worker could step in complete the process in the case of unplanned prolonged absences.

- Location of Contact Lists (study team and sites)
- How to obtain access to electronic systems
- Step by Step instructions on the use of electronic systems
- Draft before the first event is reported
- Finalize after the first event is processed
Adjudicator Training Manual

- Role of the CEC
- Member Selection Criteria/Qualifications
- Training expectations
- High Level Protocol Overview
- Overview of the Process
  - Event Identification
  - Role of the Site PI
  - Role of the CRO/ARO
  - Work Flow through the committee
- Records to Expect
Adjudicator Training Manual

- Form Completion
- GCP Training Acknowledgement
- Payments
- Questions/Contacts
- Appendix
  - Definitions
  - Forms
  - EAS Use (including step by step instructions)
Demo - Adjudicator Workflow
6.0 Follow Up and Escalation Plan

Events will be tracked based on the date of PVG notification. From this date, “aging” of events can be calculated.

Initial follow up request for required source documents to compile adjudication dossier will be completed via EDC query within 2 business days of receipt. Follow up will be re-requested every 15 days until all documents are received to compile dossier.

Day 30: CRO Safety Specialist will notify Regional CTM of outstanding documents and request assistance for query closure and document retrieval

Day 60: Safety Specialist will notify Sponsor of any events that do not have a completed dossier.

Escalation of >60 day cases include:

- PVG has continuously queried for outstanding source that has not been provided
- Unresponsive sites
- Note: Source documents require an estimated 6-8 weeks to be retrieved from sites due to dictation, records release, translation, etc.

6.1 Average Dossier Cycle Timelines

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cycle Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notification of Event</td>
<td>Day 0</td>
</tr>
<tr>
<td>Dossier Compilation</td>
<td>Day 45 – Day 65</td>
</tr>
<tr>
<td>CEC Review</td>
<td>Day 65 – Day 85</td>
</tr>
<tr>
<td>Committee Results to DM/Bio Stats</td>
<td>Immediately upon adjudication</td>
</tr>
<tr>
<td>Total</td>
<td>65 to 85 days average</td>
</tr>
</tbody>
</table>
Reports

- Payment
- Tracking
- Timeline
- Reconciliation
- Results
- Regulatory Body Requests
Demo - Reporting
Regulatory Submissions-RED Flags

- Investigator Reported Results and CEC Results go in opposite directions
- Investigator Description of Event is different from CEC or there is disagreement amongst adjudicators
Regulatory Submission-Frequent Requests

- CEC Charter and Amendments
- Entire CEC Packet with all source documents, all queries, and results of queries for the adjudicated endpoints
- SAS dataset for
  - All investigator reported events
  - All CEC adjudicated events
  - All investigator reported events that were downgraded/upgraded by CEC
Demo - Data Extraction
Case Study

- Cardiovascular outcome study of an approved urology drug due to a "signal" in another trial. Regulatory authorities are requiring the study be done. Requiring that you use definitions provided to you by the FDA.
- 300 sites (urologists) in 30 countries
- Need 600 events to complete the trial
- Oversight by a DSMB who is meeting after every 50 events
- Event types
  - Stroke
  - Myocardial Infarction
  - CV Death
  - Coronary Revascularization
Decisions

1. Is Adjudication Needed?
2. EAS vs. Paper vs. Hybrid
3. Adjudicator Qualifications
   - Availability/timelines
   - Complexity of definitions
   - Previous Experience with Adjudication
4. Process to Use
   - Number of events
   - Type of events
   - Previous experience with the definitions
   - Timelines
   - Experience/qualifications of adjudicators
Electronic Adjudication - High Level Overview

- **Site Data**
  - Event Details
  - Source Documents

- **Coordinator Review (CRO)**
  - Inventory and Review Documents
  - Create Dossier

- **Document Review (ARO)**
  - Review Documents
  - Assign Adjudicators

- **Phase 1 Adjudication**
  - Multiple Adjudicators
  - Parallel or Paired Consensus

- **Phase 2 Adjudication**
  - Additional Adjudicators
  - OR Committee

- **Phase 3 Adjudication**
  - Optional

- **Outcome**
  - Concordance
  - Notification
References


- Seltzer J. Centralized Adjudication of CV endpoints in CV and non-CV pharmacologic trials: A report from the cardiac safety research consortium. AHJ 2015.


- Walter SD. Outcome Assessment for Clinical Trials: How many adjudicators do we need? 1996 (abstract)