ARCADIA STUDY

AE/SAE Reporting Webinar
Overview

• Purpose of this presentation is to provide information and answer questions about the event reporting process for the ARCADIA study.

• For subject safety all reportable adverse events must be submitted in WebDCU™ in a timely, accurate, and verifiable manner.

• The ARCADIA study has a Medical Safety Monitor (MSM) who must review all serious adverse events within protocol determined timelines.

• Reports of SAE, Clinical Outcome Events and Events of Special Interest are submitted to Bristol-Myers Squibb (BMS) by the Clinical Event Coordinator within 72 hours of being submitted in WebDCU™.
Medical Safety Monitor (MSM)

The MSM conducts an independent review of each SAE to determine its seriousness, relationship to the study treatment, and expectedness.

In order for the MSM to review a reported SAE complete and accurate data concerning the event must be available in WebDCU™.

The MSM assessment of SAE’s is a crucial part of the ARCADIA study’s reporting to the Data Safety Monitoring Board (DSMB).
What to Report

Only events that meet the definition of a:

• SAE
• Clinical Outcome Event
• AE of Special Interest

Events that are not SAEs, Clinical Outcome Events, or Events of Interest, will not be collected or reported.
Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

• results in death;
• is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
• requires inpatient hospitalization or causes prolongation of existing hospitalization;
• results in persistent or significant disability/incapacity;
• is a congenital anomaly/birth defect;
• is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
Clinical Outcome Events
Listed on the AE CRF (Q17)

- Ischemic stroke
- Non-ischemic stroke
- Symptomatic hemorrhagic transformation of ischemic stroke
- Intracranial hemorrhage excluding either hemorrhagic stroke or symptomatic hemorrhagic transformation of ischemic stroke
- Transient ischemic attack
- Major hemorrhage excluding intracranial hemorrhage
- Minor hemorrhage
- Atrial fibrillation/flutter
- Myocardial infarction
- Systemic embolism
- Symptomatic deep venous thrombosis
- Symptomatic pulmonary embolism
- Pregnancy
- Overdose
- Potential drug-induced liver injury (DILI)
- Cancer
- Other SAE
Events of Special Interest Listed on AE CRF (Q17)

- Pregnancy—subject or partner
- Overdose—any OD, not just study medication
- Potential drug-induced liver injury (DILI)
  - Elevated LFTs suggestive of DILI
  - Report if in course of routine clinical care it is noted they become abnormal or if pre-existing abnormalities significantly worsen
- Cancer—newly diagnosed
Events of Special Interest
Listed on AE CRF (Q17)

<table>
<thead>
<tr>
<th>Q17</th>
<th>Type of event</th>
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<tbody>
<tr>
<td></td>
<td>Ischemic stroke</td>
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<tr>
<td></td>
<td>Non-ischemic stroke</td>
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<tr>
<td></td>
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<td>Cancer</td>
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<td></td>
<td>Other SAE</td>
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</table>
Reporting Adverse Events

Events are reported on the **Adverse Event Case Report Form (CRF 104)**

- Information collected on all AE includes:
  - Event Name
  - Date of onset and resolution
  - Clinician’s assessment of severity and relationship to study product
  - Detailed description or narrative of event
  - Relevant tests and laboratory data
  - Relevant history and pre-existing conditions
  - Event packet
Tips for Reporting Adverse Events

• Report only 1 event per CRF
• Report the diagnosis, not the symptoms: Fever, cough, chest pain, crackles = pneumonia
• Avoid abbreviations or colloquialisms
• Death, surgery, hospitalization, intubation, etc. are NOT names of adverse events. They are outcomes of adverse events
• Do NOT identify subject, physician or institution by name in narrative
Adverse Event Name vs AE MedDRA Term

• Adverse Event Name – free text field for you to enter the event name
• AE MedDRA Term – A list of terms from which you select the term which best corresponds with your AE Name
Reporting Timeframes

- Events should be reported from time of randomization through the end of study participation

- Events must be entered and **submitted** into WebDCU™ within **24 hours** of discovery
  - Reportable events should be updated as additional information becomes available

- Events should be followed until resolution or until 30 days after the subject’s participation in the study ends
Information to include in the narrative

Enough to give a brief, clear picture of the subject and the event.

- Age of subject
- Date of index stroke
- Date of randomization
- Date of event
- Signs/symptoms
- Significant imaging and lab tests with results
- Diagnosis
- Date study drug stopped (if appropriate)
- Date alternate anticoagulant/antiplatelet started
- Name of alternate therapy
Sample narrative for Q10

A [age] year old [male/female] was enrolled in ARCADIA on [date of enrollment]. The subject started study medication on [date]. On [date] the subject developed [symptoms] and was [admitted to hospital/taken to ED/went to PCP office]. It was determined that the patient had [Serious adverse event/disease/diagnosis]. Imaging [was/was not] obtained and were [positive/negative/results of imaging]. Other labs, ECG, Echo [were/were not] obtained and were [positive/negative/results]. [Treatments] were initiated. The patient subsequently [recovered from this event/died from this event/died from other causes before resolution of this event]. The subject stopped study drug on [date]. Study drug was restarted [date] or permanently discontinued and patient started on open label [name of medication]
Q11 Relevant tests/laboratory date including dates

Information **RELEVANT** to the event

- Relevant laboratory tests
- Relevant Imaging
- Results not needed **unless** not provided in Q10
Q12 – Other relevant history

- Relevant medical history that relates to their risk factors for stroke and related to the event that is being reported

- Possible History that should be included
  - HTN
  - Cardiovascular disease (CHF, NSTEMI, STEMI, angina)
  - Chronic renal failure
  - History of DVT
  - History of liver disease
  - History of stroke prior to index
  - Residual effects from stroke if relevant to diagnosis/event
### ARCADIA Checklist for Preparing Event Packets

Use this form as a face page, and order the Event Packet documents in the order in which they appear below. All protected health information (PHI) must be removed from the documents prior to upload.

<table>
<thead>
<tr>
<th>Category</th>
<th>Checklist Item</th>
<th>Included in packet</th>
<th>Not done</th>
<th>Done but unreviewable</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events with hospital admission</td>
<td>Admission notes</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td></td>
<td>Discharge summary</td>
<td>☑</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>All events without hospital admission</td>
<td>Notes from emergency medical services, ED, clinic, nursing home, or some combination of these regarding the event</td>
<td>☑</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>All events without healthcare contact</td>
<td>Information from patient or witnesses regarding the event</td>
<td>☐</td>
<td>☑</td>
<td>☐</td>
</tr>
</tbody>
</table>

Depending upon the type of event, also include the following:

| False events                                      | Autopsy report                                                                 | ☐                 | ☑        | ☐                     |
|                                                    | Death certificate                                                              | ☐                 | ☑        | ☐                     |
| TIA, stroke, or hemorrhagic transformation         | All head imaging reports (CT or MRI)                                          | ☐                 | ☑        | ☐                     |
|                                                    | Neurovascular imaging reports of head and neck (CTA, MRA, or angiogram)        | ☑                 | ☐        | ☑                     |
|                                                    | All operative reports for procedures on head or on vessels of the head or neck | ☑                 | ☐        | ☑                     |
| Cardiac events                                    | Cardiac enzyme reports                                                        | ☑                 | ☐        | ☐                     |
|                                                    | ECG reports                                                                    | ☑                 | ☐        | ☐                     |
|                                                    | Operative reports regarding this event, including cardiac catheterizations    | ☑                 | ☐        | ☐                     |
| Atrial fibrillation/Flutter                       | Head rhythm monitoring results                                                | ☑                 | ☐        | ☐                     |
| Major/minor hemorrhage                            | Operative reports regarding this event                                        | ☑                 | ☐        | ☐                     |
| Systemic embolization                             | Imaging reports regarding this event                                          | ☑                 | ☐        | ☐                     |
| Symptomatic PE or CIVT                            | Imaging reports regarding this event                                          | ☑                 | ☐        | ☐                     |

**Comments**
Assembling the Event Packet

• Complete the “ARCADIA Checklist for Preparing Event Packets”
• Add subject number on top of the checklist form and place form first on top of the source documents
• De-identify the source documents—look for hidden identifiers
• If imaging/ECG is relevant to the event being reported please include the radiology report or Holter monitor/rhythm strips in the packet
• Please include lab reference ranges if lab reports are relevant to the event being reported
• Scan and upload the entire packet into WebDCU™
What **not** to Include in Packet

- Completed Adverse Event Form  
  Already in WebDCU™ --don’t need another
- Source Documents that have not been completely de-identified
- Blank pages
- Pages containing no real data  
  1. Orders for tests  
  2. Hospital specific procedures
A few Comments on Event Packets

• It is helpful for the reviewers if the source documents are in chronological order.

• If more data added to the event packet, the entire packet must be uploaded as a single file.

• Only the most recent event packet is visible to the reviewers, MSM and adjudicators.
ADVERSE EVENT REPORTING Summary

Site investigators or their designees must report SAEs, clinical outcome events, and AEs of special interest through WebDCU™ within 24 hours of site awareness of the event.

The investigators are required to provide relevant information such as a description of the event, date/time of onset and resolution, severity, suspected relationship to the study treatment, and action taken.

Supporting documentation of the event should be provided as soon as possible.

Additional supporting documentation may be requested and should also be provided as soon as possible.

All SAEs, clinical outcome events, and AEs of special interest, whether related or not related to study drug, must be collected from the time of randomization through 30 days post study drug discontinuation or end of study, whichever occurs later.

All SAEs, clinical outcome events, and AEs of special interest should be followed to resolution or stabilization.
SAE vs Outcomes

- For the ARCADIA trial the **PRIMARY** outcome measurement is a subsequent stroke of any type.
- If your patient has a subsequent stroke that is confirmed, you will need to follow them for 30 days then complete the end of study CRF.
- If your patient has an SAE or AE that is not a stroke, this does not necessarily take them out of the study. Even if your patient comes off study drug, we still want to follow them in the trial for the primary outcome.
Unanticipated Event Reporting

• Clinical sites should report unanticipated events and protocol deviations in WebDCU™.

• Unanticipated events that are unexpected, related to study participation, and place the subject/others at increased risk will require prompt reporting to the CIRB. This includes any deviations involving informed consent.

• All other unanticipated events which do meet the above criteria will be reported to the CIRB at the time of continuing review.
Examples of Unanticipated Events

- LAR was used for consenting when the subject could have consented
- Short form was used when a full Spanish consent had been approved for the site
- An out of date ICF document was used
- Visit was done outside the study window/subject ran out of study medication
- Core lab tubes were drawn incorrectly or lost
Enrolled 14% (155 / 1100) of Projected Subjects

- Subject CRF Binder
- Study Progress
- Data Management
- Project Management
- Safety Monitoring
- Site Management

- Unanticipated Event Report
- Parent Protocol Continuing Review Form
- Lab Kit Shipping
- Site Lab Kit Inventory

- Drug Tracking
- Data Monitoring
- CRF Data List
- Project Setup
- User Management
- Regulatory Document

- Toolbox
- Emergency Help
How do I know if something needs to be reported promptly?

| Q03 | Was this event unexpected?  
     | (If Q03, Q04, & Q05 = yes, event meets “prompt” CIRB reporting requirements) | 〇 No  
     | 〇 Yes  |
|-----|-----------------------------------------------------------------------------|------|
| Q04 | Is this event related or possibly related to the research?  
     | (If Q03, Q04, & Q05 = yes, event meets “prompt” CIRB reporting requirements) | 〇 No  
     | 〇 Yes  |
| Q05 | Does this event suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized?  
     | (If Q03, Q04, & Q05 = yes, event meets “prompt” CIRB reporting requirements) | 〇 No  
     | 〇 Yes  |
Determining the Type of Event

Q08  Type of Event
(If any radio button except the last one is selected for this question, the event meets “prompt” CIRB reporting requirements)

- Adverse Event (s) that is/are BOTH: Unexpected and related or possibly related to participation in research. AE CRF ID: ________
- An event that may require a change to the protocol and/or consent form
- Information (including publications or sponsor report) that indicates a change to the risks or potential benefits of the research may be necessary
- Breach of confidentiality including loss of study data or computer system compromise
- Event that may indicate a need to change labeling or withdrawal from marketing for safety reasons of a drug, device, or biologic used in a research protocol
- Unapproved change to protocol made to eliminate an apparent immediate hazard to a research participant
- Protocol violation/non-compliance (either by investigator or subject) that could have caused harm or increased risk
- Incarceration of a participant in a protocol not approved to enroll prisoners
- Complaint of a participant that indicates unexpected risks or cannot be resolved by the research team
- Other unanticipated problem comparable to the events listed above
- Investigational Devices: Use of investigational device outside of the protocol for any reason
- Regulatory non-compliance issue
- OR The event/information does not fit in a category listed above and therefore does not require prompt reporting to the Central IRB and will be submitted to the CIRB at Continuing Review
What information do I need to provide?

- Explain exactly what happened
- How was it discovered
- What you did to correct the issue
- How are you going to prevent this from happening again
- Retraining is often needed
- May require a corrective action plan

| Q06 | Describe the unanticipated event in detail including date of occurrence and date of site discovery, sequence of events, actions taken (i.e., treatments given or changes in protocol defined procedures) whether the event is resolved, whether the participant remains in the study, and whether the sponsor (if applicable) has been notified. |
| Q07 | Describe the corrective measures that have been put in place to prevent similar unanticipated events |
Unanticipated Event reporting to CIRB

• Once the report has been submitted the project manager receives an email notification

• The project manager will submit to the CIRB if it requires prompt reporting-this is due within 10 days.

• The CIRB will review and send an acknowledgment letter or they may request additional information be provided.

• For events that do not trigger prompt reporting, the CIRB will pull these reports from WebDCU™ at the time of continuing review.
Contact Information

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