



OREGON CLINICAL
& TRANSLATIONAL
Research Institute

Adverse Event Management (Part 2)

DATE: December 16, 2021 PRESENTED BY: Julie Mitchell

Agenda – Part 2

- Study Documents
- Collection of Adverse Events
- Serious Adverse Events
- Frequency and Duplicate Events
- Missing Data
- Coding Events
- Reconciling Events
- Reporting
- Analysis



Study Documents

- Protocol
 - Primary and Secondary Objectives
 - Safety plan
 - Defines reportable events
 - Data analysis
- Investigator Brochure
 - Describes previous results with treatment
- Manual of Procedures (MOP)
 - Specific instructions on data entry and reporting
 - Safety assessment & reporting
 - Safety plan
- Data Safety Monitoring Plan (DSMP)
- Statistical Analysis Plan (SAP)



Study Documents

- Study documents should be comprehensive
- SAP should guide analyses including assessment of AEs
- MOP, DSMP, SAP should all be completed before collecting data



Study Documents - SAP

- Strategy to assess AEs
 - Consider which methods would best answer questions about AEs^a
 - Visualization methods (plots, graphs)
 - Hypothesis testing methods (significance testing with p-values)
 - Estimation methods (compare distributions of AEs without formal testing)
 - Decision-making probability methods (Bayesian approaches)
 - Traditional hypothesis testing is often not the best option
 - Studies tend to be designed to detect efficacy outcomes
 - Usually NOT powered for hypothesis testing for AEs (i.e., p-values)
 - Share relevant examples from the literature with your statistician



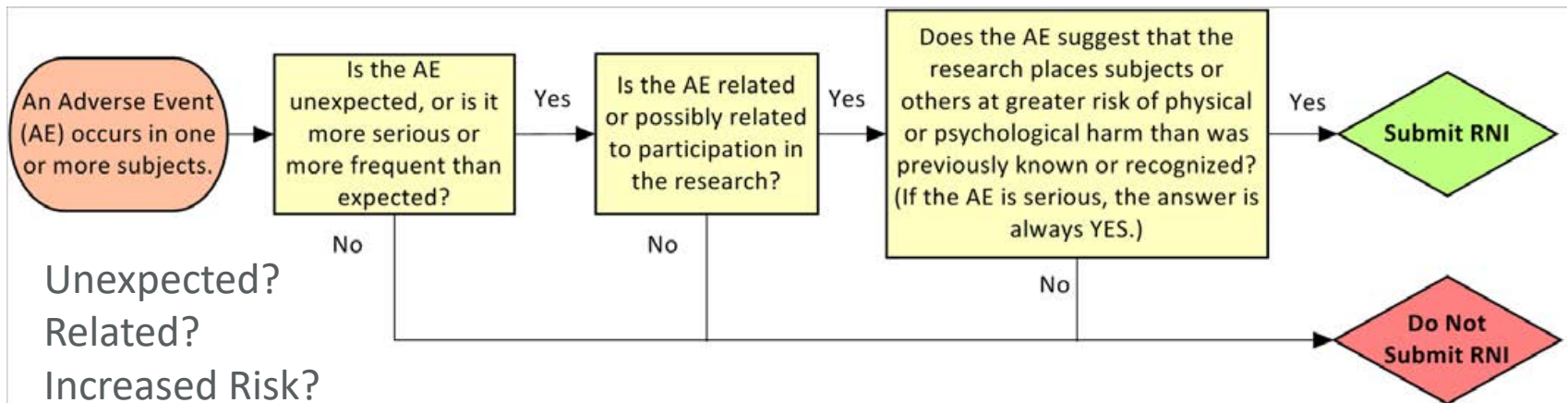
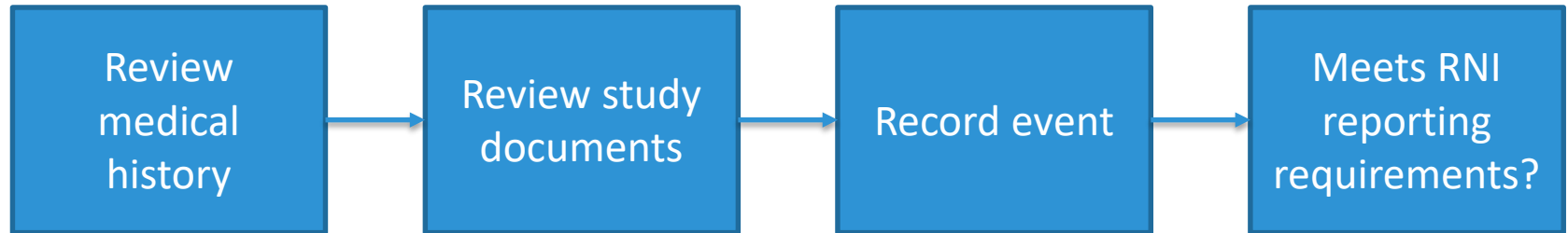
Study Documents - SAP

- Need to address the potential for unblinding
 - Plan for partial and full unblinding as the randomization scheme is set in motion
 - There is often a scramble to figure this out when data need to be unblinded



OREGON CLINICAL
& TRANSLATIONAL
Research Institute

Collection & Reporting of an Event



Collection

- How?
 - Open: Collection of all events / whatever the patient reports
 - Prompting: Asking more targeted questions
 - Direct: Useful if events are also outcomes
 - Mix
- When?
 - During any interaction with participant or source document
- Where?
 - Pre-baseline
 - During study conduct



Adverse Event Fields to Collect

- Fields to include:
 - Event (diagnosis/ unifying diagnosis or symptoms?)
 - Start date
 - Stop date
 - Outcome
 - Severity
 - Relatedness
 - Actions Taken (treatment)
 - Expected?
 - Intermittent?
 - Ongoing?
 - Seriousness yes – review medical record for event and collection of additional information for SAE Narrative)
 - *Medical Code*
 - *Reportable?*
 - *Date reported (if RNI)*
 - *Date Reported (may be in an audit log)*

Record additional details in source documents

Adverse Event Log

Recommend collecting/ consolidating events in a log format

ADVERSE EVENTS LOG (HAND ENTRY)										
Complete for randomized subjects										
☐ 1. No AEs to report <i>checkbox</i> Table below not displayed if box is checked										Page of
Row	2a. Verbatim Description <i>text</i>	2b. DCC Completed MedDRA Code <i>lookup</i>	2c. Onset Date & Time <i>date & time</i> (dd-mmm-yyyy 24hr) and 2d. Intermittent <i>checkbox</i>	2e. Severity <i>radio</i> Refer to option list below	2f. Relationship to Study Drug <i>radio</i> Refer to option list below	2g. Action Taken <i>checkbox</i> (1 or more) Refer to option list below	2h. Resolution Date & Time <i>date</i> (DD-MMM-YYYY 24hr)	2i. Outcome <i>radio</i> Refer to option list below	2j. SAE <i>radio</i>	2k. Expected? <i>Radio only</i> (1/2) & yes 2j. Documentation for SAE <i>file attachment</i>
1			DDMMYY HH:M ☐ Intermittent				DDMMYY HH:M		☐ Yes ☐ No	☐ Yes ☐ No
2			DDMMYY HH:M ☐ Intermittent				DDMMYY HH:M		☐ Yes ☐ No	☐ Yes ☐ No
3			DDMMYY HH:M ☐ Intermittent				DDMMYY HH:M		☐ Yes ☐ No	☐ Yes ☐ No
4			DDMMYY HH:M ☐ Intermittent				DDMMYY HH:M		☐ Yes ☐ No	☐ Yes ☐ No
5			DDMMYY HH:M ☐ Intermittent				DDMMYY HH:M		☐ Yes ☐ No	☐ Yes ☐ No

SEVERITY	RELATIONSHIP TO DRUG	ACTION TAKEN	OUTCOME
1 Mild	1 Definitely related	0 None	1 Resolved
2 Moderate	2 Probably related	1 Medical Intervention	2 Recovered with minor sequelae
3 Severe	0 Unrelated	2 Hospitalization (after initial discharge)	3 Recovered with major sequelae
		3 Hospitalization prolonged	4 Ongoing/ Continuing treatment
		4 Concomitant Medication	5 Condition Worsening
		5 Concomitant Therapy	6 Death
		99 Other <i>Specify text</i>	99 Unknown



OREGON CLINICAL
& TRANSLATIONAL
Research Institute

Serious Adverse Event

- Review medical record for details
- Collection of additional information beyond what is required for AEs
- Consider recording SAE's on the standard AE form
- Document the process for notification to the PI/ coordinating center

Serious Adverse Event Form

Serious Adverse Event (SAE) Report Form	
Protocol Title: _____	
Protocol Number: _____	
Site Number: _____	
Pt_ID: _____	
1. SAE Onset Date: _____ (dd/mm/yyyy)	
2. SAE Stop Date: _____ (dd/mm/yyyy)	
3. Location of serious adverse event (e.g. at study site or elsewhere): _____	
4. Was this an unexpected adverse event? ☐ Yes ☐ No	
5. Brief description of participant with no personal identifiers: Sex: ☐ Female ☐ Male Age: _____	
6. Adverse Event Term(s): _____ _____	
7. Brief description of the nature of the serious adverse event (attach description if more space needed): lkfdssdgdasg adglm'grekm _____	
8. Category of the serious adverse event:	
☐ death – date _____ (dd/mm/yyyy) ☐ life-threatening ☐ hospitalization - initial or prolonged ☐ disability / incapacity	☐ congenital anomaly / birth defect ☐ required intervention to prevent permanent impairment ☐ other: _____
Serious Adverse Event Report Form 1 of 2 Version 1.1	

Serious Adverse Event (SAE) Report Form	
9. Intervention type:	
☐ Medication or Nutritional Supplement: specify _____ ☐ Device: Specify: _____ ☐ Surgery: Specify: _____ ☐ Behavioral/Life Style: Specify: _____	
10. Relationship of event to intervention:	
☐ Unrelated (clearly not related to the intervention) ☐ Possible (may be related to intervention) ☐ Definite (clearly related to intervention)	
11. Was study intervention discontinued due to event? ☐ Yes ☐ No	
12. What medications or other steps were taken to treat serious adverse event? _____ _____	
13. List any relevant tests, laboratory data, history, including preexisting medical conditions _____ _____	
14. Type of report:	
☐ Initial ☐ Follow-up ☐ Final	
Signature of Principal Investigator: _____ Date: _____ (dd/mm/yyyy)	
Serious Adverse Event Report Form 2 of 2 Version 1.1	

https://www.nia.nih.gov/sites/default/files/adverse_events_form.pdf



**OREGON CLINICAL
& TRANSLATIONAL**
Research Institute

Advantages for Standardizing Data Collection

- Allows comparisons across studies (within a similar indication or treatment)
- Ease of submission to a department repository
- Sharing data externally

Frequency & Duplicate Events

- What to do if the same event occurs more than once?
 - ‘intermittent’ vs. separate events
- What do you do if the information changes over time (example: a closed event turns out to be intermittent?)

Example:

Participant reported having multiple headaches after joining the study. In a review of their medical history the participant had listed headaches. When asked additional details the participant disclosed that prior to starting the study he had around 1 headache per month. They now are having at least a headache once a week that have not changed in severity.

Frequency & Duplicate Events

Events that are NOT linked pathophysiologically, or temporarily, need to be reported as separate events

Example:

Participant is admitted to the hospital with Heart Failure. Then develops sepsis while in the hospital as a result of the venous catheter and this prolongs the hospitalization.

A new event should be created for AE's the increase in severity. Do not create a new event as an AE resolves (severity decreases).

Missing Data

- If missing information or clarification is required, document all attempts to gather missing information. Continue until study is locked.
- If expedited reporting – update missing or incorrect information in secondary report



Coding Adverse Events

- Determine coder
 - Coordinating center
 - PI
 - Local site
- For multi-site:
 - Consider a single coder – allows standardization. But details are required!
- If open text is used for AE description, then it must be coded at some point.

Coding Events

- Determine coding ontology/ dictionary to utilize for Medical History and AEs
 - ICD-9-CM and HARTS
 - CTCAE
 - MedDRA
- Dictionaries can be updated – use a single version
- Individual(s) performing coding should have appropriate training
- Study teams should develop a reliable, unbiased and reproducible process so that safety is not compromised

Coding Events

- Effective Coding Requires:
 - Good system
 - Good data collection practices
 - Coding/Auto coding
 - Data Managers
 - Coding Experts
 - Statistician input
- Performed throughout study

Reconciling Events

Details, details, details.

- Review coding (i.e. grouping to medical terms)
- May require review of medical records
- When an AE is an outcome...
 - Talk with your statistician and consult your Statistical Analysis Plan (much more detailed then the statistical section in your protocol)

Example:

Joint pain, knee pain, aching knee may all be the same kind of event. Also expect that drugs used to treat knee pain should be the similar

Reporting

Look at the content of reporting requirements

- IRB (RNI)
- Other Institutional Committees
- Safety
- NIH
- FDA
- Other study staff (e.g. statistician)

Plan Report Format

- NIH clinical trial: DSMP required by NIH
- Knight Cancer Institute: Knight DSMP
- Other: IRB DSMP

Safety Reporting

- Plan on time – don't try to generate safety reports in an hour and be done!
- Consider blinding – a double blinded study may require multiple reports and an individual that is unblinded

Remember to BUDGET for these activities



OREGON CLINICAL
& TRANSLATIONAL
Research Institute

Safety Reporting

- Build and run reports as outlined in your DSMP
- Types of Reports:
 - Expedited reporting for RNI's (as needed)
 - Continuing Review (Annual)
 - Safety Monitoring Reports (dependent on risk)
- Save and utilize a single dataset for each safety report.

Safety Report

Body System and Preferred Term	A				B			
	Mild $\frac{n_{\text{e}}^{(2)}(n_{\text{u}})^{(3)}}{[>1]^{(4)}}$	Moderate $\frac{n_{\text{e}}^{(2)}(n_{\text{u}})^{(3)}}{[>1]^{(4)}}$	Severe $\frac{n_{\text{e}}^{(2)}(n_{\text{u}})^{(3)}}{[>1]^{(4)}}$	Total $\frac{n_{\text{e}}^{(2)}(n_{\text{u}})^{(3)}}{[>1]^{(4)}}$	Mild $\frac{n_{\text{e}}^{(2)}(n_{\text{u}})^{(3)}}{[>1]^{(4)}}$	Moderate $\frac{n_{\text{e}}^{(2)}(n_{\text{u}})^{(3)}}{[>1]^{(4)}}$	Severe $\frac{n_{\text{e}}^{(2)}(n_{\text{u}})^{(3)}}{[>1]^{(4)}}$	Total $\frac{n_{\text{e}}^{(2)}(n_{\text{u}})^{(3)}}{[>1]^{(4)}}$
Term								
Total	38 (13) [7]	23 (9) [4]	10 (4) [1]	71 (21) [11]	56 (26) [9]	32 (12) [5]	8 (4) [0]	96 (32) [18]
Cardiac disorders (10007541)	----	1 (1) [0]	----	1 (1) [0]	----	1 (1) [0]	----	1 (1) [0]
Palpitations (10033557)	----	----	----	----	----	1 (1) [0]	----	1 (1) [0]
Tachycardia paroxysmal (10043079)	----	1 (1) [0]	----	1 (1) [0]	----	----	----	----
Eye disorders (10015919)	----	----	----	----	----	1 (1) [0]	----	1 (1) [0]
Retinal vein occlusion (10038907)	----	----	----	----	----	1 (1) [0]	----	1 (1) [0]
Gastrointestinal disorders (10017947)	4 (4) [0]	3 (3) [0]	1 (1) [0]	8 (8) [0]	18 (10) [3]	8 (7) [1]	2 (1) [1]	28 (16) [7]
Abdominal distension (10000060)	----	----	----	----	2 (1) [1]	----	----	2 (1) [1]
Abdominal pain (10000081)	1 (1) [0]	1 (1) [0]	----	2 (2) [0]	1 (1) [0]	1 (1) [0]	----	2 (2) [0]
Clostridium difficile colitis (10009657)	----	----	----	----	----	----	2 (1) [1]	2 (1) [1]
Constipation (10010774)	----	1 (1) [0]	----	1 (1) [0]	----	----	----	----
Diarrhoea (10012735)	1 (1) [0]	----	----	1 (1) [0]	----	1 (1) [0]	----	1 (1) [0]
Dysgeusia (10013911)	----	----	----	----	1 (1) [0]	----	----	1 (1) [0]
Dyspepsia (10013946)	----	----	----	----	5 (5) [0]	----	----	5 (5) [0]
Flatulence (10016766)	1 (1) [0]	----	----	1 (1) [0]	2 (1) [1]	----	----	2 (1) [1]
Gastroenteritis viral (10017918)	----	----	----	----	----	1 (1) [0]	----	1 (1) [0]
Gastroesophageal reflux (10017885)	----	----	----	----	1 (1) [0]	2 (2) [0]	----	3 (2) [1]
Gastrointestinal haemorrhage (10017955)	----	----	1 (1) [0]	1 (1) [0]	----	----	----	----
Nausea (10028813)	1 (1) [0]	1 (1) [0]	----	2 (2) [0]	4 (4) [0]	2 (2) [0]	----	6 (6) [0]
Vomiting (10047700)	----	----	----	----	2 (2) [0]	1 (1) [0]	----	3 (3) [0]
General disorders and administration site conditions (10018065)	----	----	----	----	1 (1) [0]	----	----	1 (1) [0]
Non-cardiac chest pain (10062501)	----	----	----	----	1 (1) [0]	----	----	1 (1) [0]
Hepatobiliary disorders (10019805)	----	----	----	----	1 (1) [0]	----	----	1 (1) [0]
Cholecystitis (10008612)	----	----	----	----	1 (1) [0]	----	----	1 (1) [0]

23 (9) [4]

Every cell has the following:

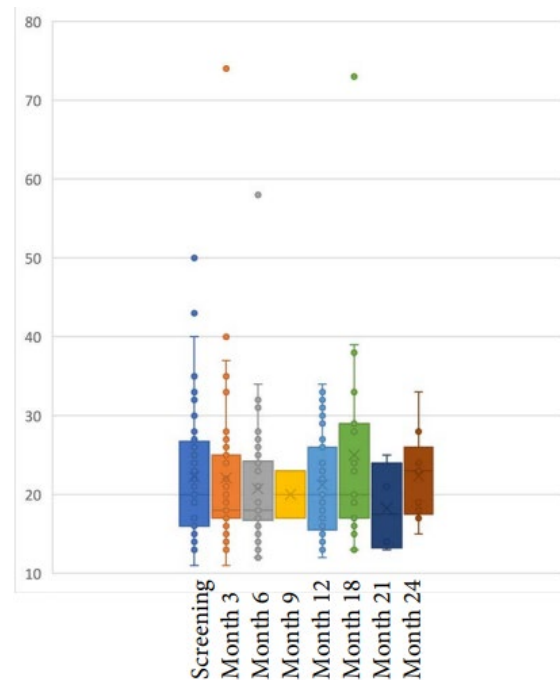
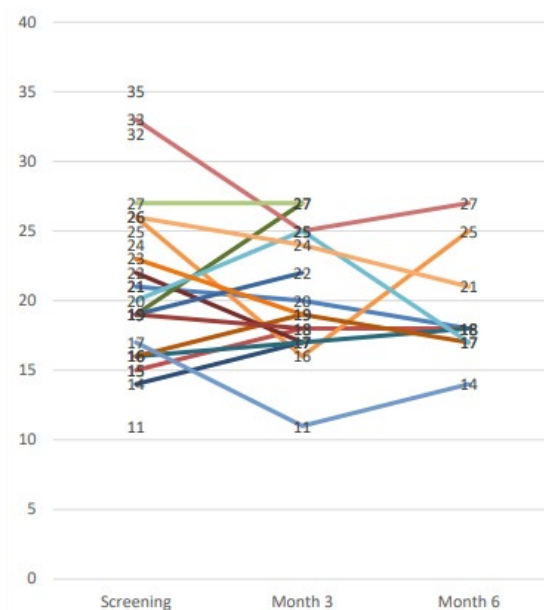
- Number of events
- () Number of unique participants experience the event
- [] Number of participants with more than 1 event



OREGON CLINICAL
& TRANSLATIONAL
Research Institute

Laboratory Safety Report

- Consider Scatter Plot or a Box Plot (may be dependent on number of observations). Also provide Mean, Median, Min, Max, SD and count



General Safety Reporting Tips

- If in doubt, report
- Meet required reporting time limits - report with available information (do not wait for additional information or confirmation)
- If a cascade of events, report with a unifying diagnosis, not each individual symptom

Correcting Safety Reports

- It's okay to update and correct errors in prior reports
- Be transparent with corrections and what is currently known

Potential Consequences of Underreporting

- Suspension of funding
 - Investigator
 - Institution
- Suspension of ability to conduct research at institution
- Disqualification
- If due to falsification:
 - Criminal penalties
 - Disbarment
- Closure of all University clinical research

Analysis

- How will you plan on evaluating AEs (by age, sex, disease)?
Look at your end points and talk to your statistician
- Consider blinding. Is your study double blinded? If so you may need someone independent from your immediate study team to produce your safety reports.
- Review your Statistical Analysis Plan
- For multi-site:
 - Consider a single coder – allows standardization. But details are required!
- Determine coding ontology/dictionary to utilize for Medical History and AEs
- Coding requires appropriate medical knowledge and designation by the PI



Common Issues to Look For

- Person(s) assessing event is not qualified to do so – not on study protocol, insufficient or no medical training, no licensing... etc.
- Lacking detailed descriptions – not able to code
- Events not appropriately documented – Ex: date of occurrence vs. date site aware
- Event not reported to FDA and/or IRB in required timeframe
- Reporting timeframe requirements not met
- Protocol-specified study procedures not followed

Communicate with your Statistician

- Your statistician should be current on what's happening in the trial
 - Discussing drop-out is especially important for AE analysis and reporting
- Investigators should help contextualize AEs for their statistician
 - Provide frequency of AE outside study and/or from related trials
 - Share information from earlier phases of the trial if available





OREGON CLINICAL
& TRANSLATIONAL
Research Institute

Thank You

References

- [NIH Data and Safety Monitoring](#)
 - NIH Policy for Data and Safety Monitoring
 - Data and Safety Monitoring for Phase I and Phase II Trials
 - Institute/Center Procedures and Guidance
- [Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance \(2007\)](#)
- [NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH Supported Multi-Center Clinical Trials](#)
- Phillips, R., Sauzet, O. & Cornelius, V. Statistical methods for the analysis of adverse event data in randomised controlled trials: a scoping review and taxonomy. *BMC Med Res Methodol* **20**, 288 (2020). <https://doi.org/10.1186/s12874-020-01167-9>

OHSU Resources

- [OHSU IRB Policies and Forms](#)
 - OHSU Reportable New Information Quick Guide
 - OHSU Reportable New Information – FAQ
- [OHSU Subject Injury Reporting](#)– CRSO
 - OHSU Position Statement
 - OHSU Consent Liability Statements
 - Subject Injury Reporting Procedure
 - Reporting Flowcharts
- OCTRI Education
 - [eLearning: Research Subject Injuries: Identification and Reporting at OHSU](#) (in Compass)
 - OCTRI Research Forum – Subject Injury Policy, Identification and Reporting
 - Additional eLearning coming soon for RNI's
- OHSU RNI Resources
 - [Reportable New Information \(Quick Guide\)](#)
 - [Reportable New Information - Frequently Asked Questions \(FAQ\)](#)

Other Resources

- MedDRA published case studies of MedDRA use in Academics
 - <https://www.meddra.org/academia>
- [MedDRA coding presentation for AEs](#)