NRG ONCOLOGY

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NRG Protocol Support Committee Discuss With Us

Adverse Event Reporting

Wednesday, November 19, 2025

NCI National Clinical Trials Network
a National Cancer Institute program

NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

Presenters & Disclosures

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No disclosures for any of the presenters

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What is an Adverse Event (A/E)

Why we report A/E's

The Steps in A/E reporting

Expedited AE reporting

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Adverse Event Defined

- **ICH, GCP AND OHRP DEFINITION:**

  Any unfavorable or unintended SIGN, SYMPTOM, DISEASE, ABNORMAL LAB, which was absent at baseline or worsened AND is temporally associated with medical treatment or procedure, REGARDLESS of attribution (i.e., relationship of event to medical treatment or procedure

- **FDA DEFINITION OF ADVERSE EVENT:**

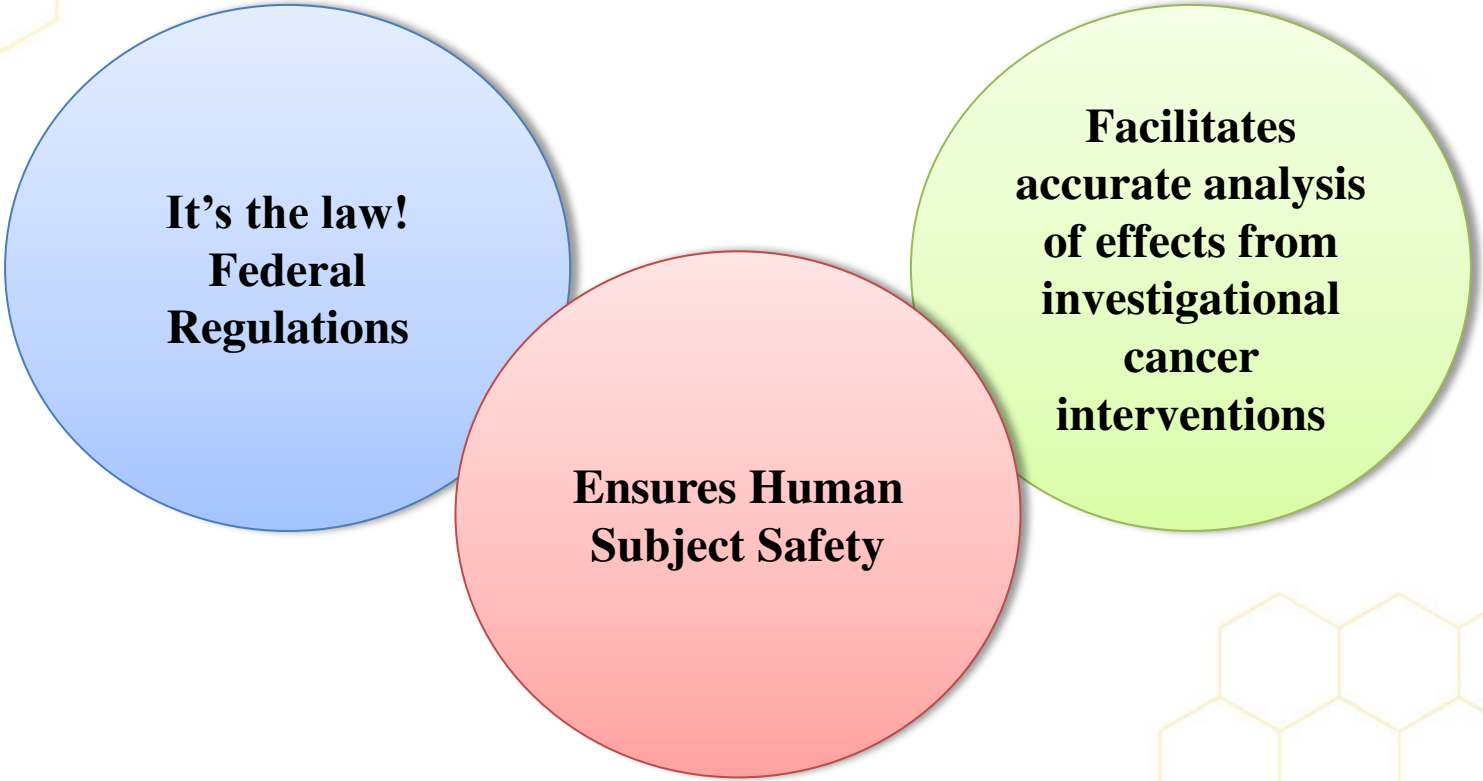
  Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related

WHAT IS AN ADVERSE EVENT?

AE'S CAN BE:

- Symptomatic or completely asymptomatic
- Clinically or radiographically detected
- Noted on laboratory studies or other testing
- Can be subjective

WHY REPORT AE'S?



Unique Issues in Cancer Trials

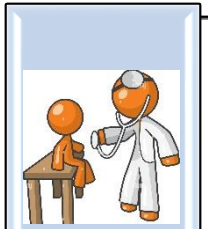
It can be very difficult to accurately report and assess AEs.

- Cancer protocols often include multiple study drugs or treatment modalities
- Prior anti-cancer therapy can affect the incidence or severity of an AE observed while on study
- The subject's cancer or other comorbidities and concomitant medications can affect the incidence or severity of an AE observed while on study

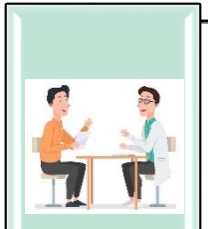
Steps In Adverse Event Reporting

Step	Task	Resources
1	Assess the adverse event	Subject interview Subject examination Medical records
2	Determine terminology and grade	Applicable version of the CTCAE
3	Determine attribution and expectedness	Protocol Investigators Brochure Consent form
4	Document the adverse event	https://ctep.cancer.gov/protocolDevelopment/eletctronic_applications/docs/aeguidleines.pdf
5	Determine expedited reporting requirements	Protocol CRFs FDA/CTEP reporting requirements

Step 1: Assess the Adverse Events



The Research Nurse/Coordinator & treating physician, assesses the patient at each visit for adverse events since last visit.



Ideally, AE's should be spontaneously reported or elicited from a subject:

*During open-ended questioning (solicited)

*During examination and evaluation

Also review:

1) Medical records to include notes and test results from other health providers

2) Subject Diaries / QOL's

NOTE: do not CTCAE code/grade PRO responses

Question: Safety is often a key objective used to assess toxicity in clinical trials. How do investigators assess safety?

a) Adverse Events
b) Subject Diaries
c) Investigator's Brochure
d) Package Insert

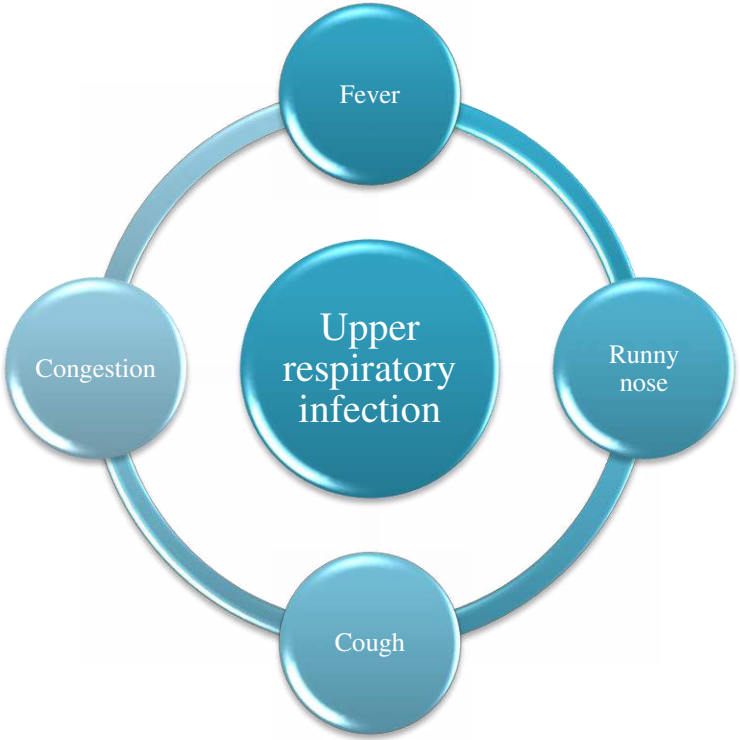
Answer: A

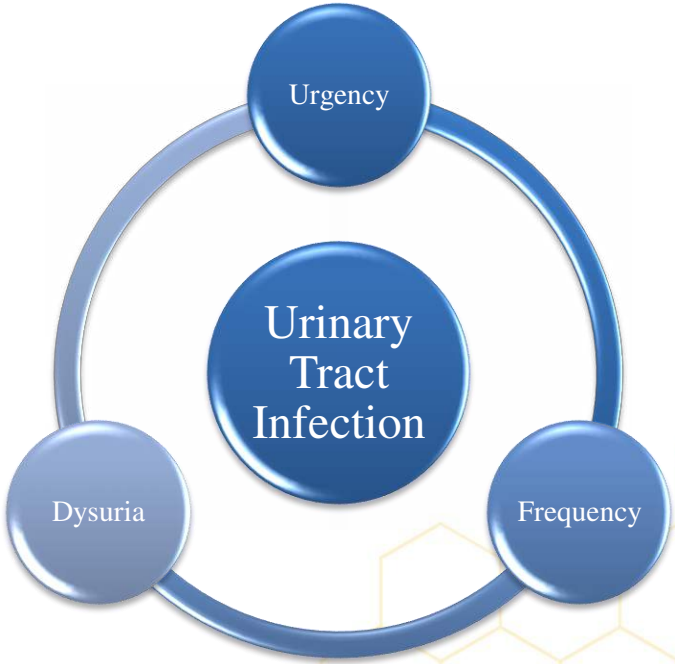
- Monitoring, collecting, documenting and reporting AEs is a major way that we monitor safety in clinical research.

Important Things to Note:

1. **Know/document the subject's baseline status and medical conditions** so you can determine any changes and note findings
   - Some events are graded as increase/decrease from baseline (i.e. diarrhea)
2. **AE reporting in study database typically starts at the initiation of the protocol therapy; report all AEs (all grades) regardless of relationship to protocol treatment**
   - In follow-up (typically > 30 days from end of protocol treatment) only report related AEs
   - Continue to follow ongoing AEs until resolution or resolved with sequela **Some protocols require key solicited AEs if present or not.**
3. **Streamlined versus IND studies**
4. **Capture DIAGNOSIS vs. SYMPTOMS**

Diagnosis Verses Symptoms





Laboratory abnormalities and changes in vital signs (outside of reference ranges) are considered adverse events if resulted in any of the following:

- Discontinuation or interruption of study treatment.
- Clinically significant per investigator assessment.
- Require therapeutic medical intervention.
- Meet protocol specific criteria (see toxicity management in protocol)
- If the investigator considers them to be adverse events.

Streamlined Clinical Trials

- Late Phase, CTEP-sponsored, IND exempt treatment trials
- Limit AE reporting in the clinical trial data base to Grade 3 or greater; do not report attribution; no start/end dates.
  - Does not change local collection or assessment.
- Other implications:
  - Finite AE reporting in follow-up
  - Limited Expedited reporting requirements

Step 2: Determine the Term and Grade

Common Terminology Criteria for Adverse Events (CTCAE)

- Current Version 5.0 (published Nov, 2017). Version 6.0 published, pending implementation in 2026
  - Note: CTEP-AERS will accommodate both v.5 and v.6; studies activated in v.5 will continue to report in CTEP-AERS in v.5
- Coding dictionary: operationally define, code, and grade AE's
  - **Promotes standardization for AE data reporting within oncology research**
- Facilitates a common understanding of AE data shared among academic, commercial and regulatory entities
- Assists in defining oncology research protocol parameters (such as eligibility criteria, dose limiting toxicity, maximum tolerated dose, dose modification, etc.)

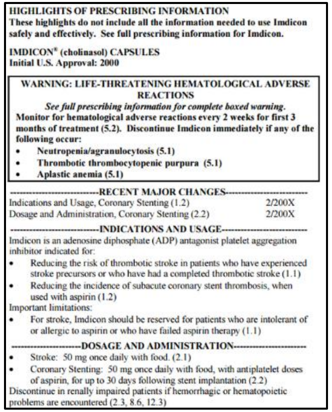
CTCAE Grade: Severity (not seriousness) of event

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Step 3: Determine Attribution & Expectedness

Attribution

- Relationship between AE and protocol treatment
  - Unrelated: unrelated, unlikely
  - Related: possible, probable, definite
- *Determined by the physician*



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS
See full prescribing information for complete boxed warning.
Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:
- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

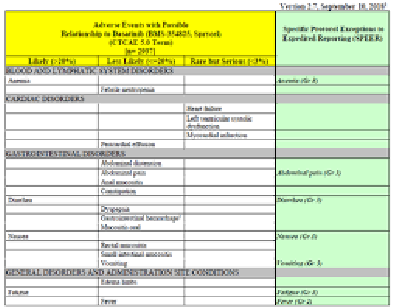
---RECENT MAJOR CHANGES---
Indications and Usage, Coronary Stenting (1.2) 2/200X
Dosage and Administration, Coronary Stenting (2.2) 2/200X

---INDICATIONS AND USAGE---
Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:
- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:
- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

---DOSAGE AND ADMINISTRATION---
- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)



Version 2.7, September 10, 2018

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			*Anemia (Gr 3)*
	Febrile neutropenia		
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Pericardial effusion		
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		*Abdominal pain (Gr 3)*
	Anal mucositis		
	Constipation		
Diarrhea			*Diarrhea (Gr 3)*
	Dyspepsia		
	Gastrointestinal hemorrhage		
	Mucositis oral		
Nausea			*Nausea (Gr 3)*
	Rectal mucositis		
	Small intestinal mucositis		
	Vomiting		*Vomiting (Gr 3)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			*Fatigue (Gr 3)*
	Fever		*Fever (Gr 2)*

Expectedness

- Package inserts
- Investigator's Brochure (IB)
- Comprehensive Adverse Event and Potential Risks (CAEPR) list
- Informed consent document

Attribution Description

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly* ***NOT*** *related* to the intervention
	Unlikely	The AE *is* ***doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

Step 4: Document the Event in Progress Note and AE Log

1. **All AE's should be collected in source documents without regard to attribution, including workup or treatment required.**
2. Good progress notes contain both good clinical practice documentation and good clinical research practice documentation including:
   a. Date the AE began (may need time if related to dosing)
   b. Treatment for the AE
   c. Description of the Event in enough detail that a CTCAE term and grade can be assigned (e.g. noting # bowel movements for diarrhea)
   d. Attribution of the AE
   e. Date the AE resolved
3. If AE worsens or improves in severity or relationship changes, documentation should be collected
4. **Supports the AE information submitted to Rave**

Step 5: Expedited Adverse Event Reporting

1. In addition to Routine AE reporting in Rave
2. Follow the Protocol requirements, also know your institutional requirements, for **expedited reporting**:
   - Seriousness criteria
   - Which grades must be reported
   - What is the timeline for reporting, 24 hours, 5-days, 10 days, etc.?
   - Are there any inclusions/exclusions to reporting?
   - Is it reportable to the IRB? (report per institutional policy)

Serious Adverse Events

Results in one of the following outcomes:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization (> 24 hours)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Import Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6)

Protocol Expedited Reporting Table

7.4.2.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2] (24-SEP-2024)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

Other Protocol Expedited Reporting Requirements

- AEs of Special Interest (AESI)
- Exclusions to expedited reporting (e.g. SPEER)
- SOC v IND arms
- FDA IND Reporting: unexpected and related SAEs

Question: Does Grade 3 platelet count decrease, require expedited reporting in CTEP-AERS?

a) True
b) False
c) Depends

Answer: C

- Does it meet one of the six seriousness criteria? Refer to the protocol for expedited reporting requirements.

CAEPR: comprehensive adverse events and potential risks

- is an NCI-generated list of reported and/or potential AEs associated with an investigational agent currently under an NCI IND/IDE. Information contained in the CAEPR is compiled from the Investigator's Brochure (IB), the Package Insert (for those investigational agents that are available commercially), the Instructions for Use (IFU - for a device), as well as company safety reports and AEs submitted through CTEP-AERS.

SPEER: specific protocol exceptions to expedited reporting

- AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS **ONLY IF** they exceed the grade of the event listed in parentheses after the event. If the SPEER is part of a study that uses multiple investigational agents and the same AE is listed on the multiple SPEERs, use the lower of the grades to determine if expedited reporting is required. The SPEER is only used for investigational agents in CTEP IND studies.

EXAMPLE: CAEPR with SPEER for Pembrolizumab

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain Colitis[2] Diarrhea[2] Mucositis oral[2]		*Diarrhea[2] (Gr 2)*
	Nausea		*Nausea (Gr 2)*
	Pancreatitis[2]		
	Small intestinal mucositis[2]		

How to report an SAE

- Follow institutional guidelines for notification to your IRB.
- CTEP-AERS directly or via Rave-CTEP-AERS integration
  - IND Studies: 24-hour notification followed by a complete report within 5 or 10 days.
  - Non-IND Studies: 15 day report
  - Rules Evaluation (RE): a recommendation, not a mandate
- CTEP-AERS is integrated with the Source Document Portal (SDP):
  - Deidentified supporting source documentation should be uploaded to the SDP via the CTEP-AERS integration (include the protocol number, patient ID number, and CTEP-AERS ticket number on each page).

References

- CTEP-AERS website:

https://ctepcore.nci.nih.gov/ctepaers/security/login

- NCI Adverse Event Reporting Requirements:
https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/reporting-requirements.pdf

- CTEP-AERS Training Slides:

https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/aers-training-slides.pdf

- NRG Oncology Routine AE reporting Guidelines:

https://www.nrgoncology.org/Portals/0/About%20Us/Policies/Routine%20AE%20Reporting%20Guidelines_v.03%20Jan%202023.pdf?ver=XXXozJNiL5_rQOh_umFrGw%3d%3d

Questions?

Acknowledgements

Thank you for all that you do for clinical trials and the patients!

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