THE ROCKEFELLER UNIVERSITY HOSPITAL

CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE

ADVERSE EVENTS
Not good,
Not bad,
Just the facts!

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Learning Objectives

To be able to:

- articulate what constitutes a potential adverse event
- list 3 reasons that recognizing adverse events is important
- identify and record the information that the research team will need for reporting and tracking

Adverse Events

- Any untoward medical occurrence in a research subject which may or may not have a causal relationship with the study
- All events will be reported regardless of whether thought to be associated with the study
- Any change to the participant's 'baseline'

AE's Include:

- After signing consent, any change in:
  - pre-existing condition
  - new onset or worsening sign, symptom, syndrome, or illness
  - laboratory finding
  - EKG
  - Other evaluations

Adverse Events ???

- Drop in hemoglobin level
- Skin rash
- Headache
- Loss of appetite
- Weight gain
- Fall on the hill to RU
- Asthma attack
- Tooth extraction
- Broken leg when hit by taxi

Why is Recognizing AEs Important?

- Safety
- Protocol integrity
- Compliance with the protocol
  - Tracking, classifying, grading, attributing, follow-up, closing
- Reporting
- Changes to risk/benefit ratio
- Changes in participant's willingness to consent

How Do You Elicit AE's?

- Ask the participant:
  - Have there been any changes in your health since your last visit?
  - Have there been any changes in your medications?
  - Do NOT suggest AE's

Think of It as a STORY

- What happened
- Get the facts
  - When did it start/stop? Continuing? Over? (dates)
  - What else was happening? Did it occur after starting the study drug? Procedure?
  - Nature/intensity – missed work?
  - Need details of treatment, dates, doses, etc
  - Need outcome; over? Sequelae? Recurring?

Sample Documentation of AE

- Participant states that nausea and vomiting started 6/5/2013, at 10am, shortly after starting his first does of the study medication. The vomiting was over by about 5pm, however, diarrhea started at about 2pm. He doesn't think he had fever. He did not take any medications. He felt so light headed by evening that he called in sick to his evening shift for work and slept poorly. His roommate gave him lomotil to help with diarrhea.
- He did not take the 6pm study drug dose on 6/5, or the 10am dose of 6/6 because he was not sure whether he should.
- He also reports he had attended a picnic the evening before (6/4), and says that the potato salad tasted a little 'off'.

If There Has Been a Change in a Medication……

- The reason for the medication change must be documented (it *might* be an adverse event!)
  - if a drug dose was changed, why? Worse? Better?
  - If a drug is added, what changed in the participant' baseline?
    - E.g. Tylenol for h/a; the h/a is an AE
    - E.g. Cardizem dose increased for BP; change = AE
- Reconciliation of concomitant medication list is an opportunity to identify AEs

What Happens Next?

The research team needs enough information to complete Classification and Reporting:

- Federal definition of “Serious adverse event”
- Anticipated vs Unanticipated

- Category
- Grade
- Attribution (relatedness)
- Tracking and reporting (entry into iRIS)
- Completion of CRF
- Reconciliation during monitoring/audits

Categories

- Serious AE
- Non-serious AE
- Anticipated
- Unanticipated

Serious Adverse Event (SAE)

- Death
- Life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

- 21CFR 312.32
- ICH GCP 1.50

Serious Adverse Events???

- Infected IV site requiring antibiotics ?
- Pneumonia after research bronchoscopy ?
- Elective hip replacement surgery ?
- Nausea requiring inpatient hydration ?
- Myocardial Infarction (heart attack) ?
- Stroke ?

"Anticipated" Adverse Events

- Any adverse event that is listed in the Investigator's Brochure, package insert, safety reports, clinical protocol, informed consent form, or the NCI agent-specific Expected Adverse Event List, is classified as an anticipated adverse event.
- The investigator must provide the available data of known adverse events and toxicities that have been associated with the study drug, device, intervention, or procedures to the IRB in the protocol and associated documents.

Unanticipated Adverse Event (UAE)

- Any adverse event that is not consistent with the known, predicted effects of the research protocol.
- An unanticipated adverse event varies in nature, intensity or frequency from information on the investigational product in the Investigator's Brochure, package insert, safety reports, clinical protocol, or informed consent form.

If Unanticipated:

Evaluate:

- Does the risk/benefit ratio change?
- Do current participants need to be notified?
- Do previous participants need to be notified?
- Does the consent need to be amended?
- Does the protocol need to be amended?
- Does the IB need to be amended?

Other Problems that Need to Be Reported w/in 5 days:

- Any unanticipated problems or deviations from protocol conduct involving or creating more than minimal risk to subjects or others, or irregularities in the process of informed consent
- Physical or emotional harm to the subject during the execution of the experimental protocol
- A breach of confidentiality or privacy
- Unexpected harmful effects of an investigational or FDA-approved drug, biologic or device, observed in other research settings similar to that of the approved project.

Classification: AE Category

- CTCAE v3.0 (http://ctep.info.nih.gov/reporting/ctc.html)

- CTCAE v4.0 (http://ctep.info.nih.gov/reporting/ctc.html)

- AIDS Clinical Trials Group (http://aactg.s-3.com)

AE Category

Classification: AE Grade

0 **No AE** or within normal limits

1 **Mild AE** - minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance

2 **Moderate AE** - minimal intervention; local intervention; noninvasive intervention [packing, cautery]

3 **Severe AE** - significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation

4 **Life-threatening or disabling AE** - complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation

5 **Fatal AE**

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death

Classification: Adverse Event Attribution (determined by PI or LIP on the study)

1. **Related** The AE *is **clearly** related* to the intervention
2. **Probable** The AE *is **likely** related* to the intervention
3. **Possible** The AE ***may be** related* to the intervention
4. **Not likely** The AE *is **doubtfully** related* to the intervention
5. **Not related** The AE *is definitely **NOT** related* to the intervention

- NCI Jan 2005

Tracking Adverse Events in IRIS

- Where are AE s tracked?
- Who tracks them?
- How do you read them?
  - Initial reports
  - Follow-up reports

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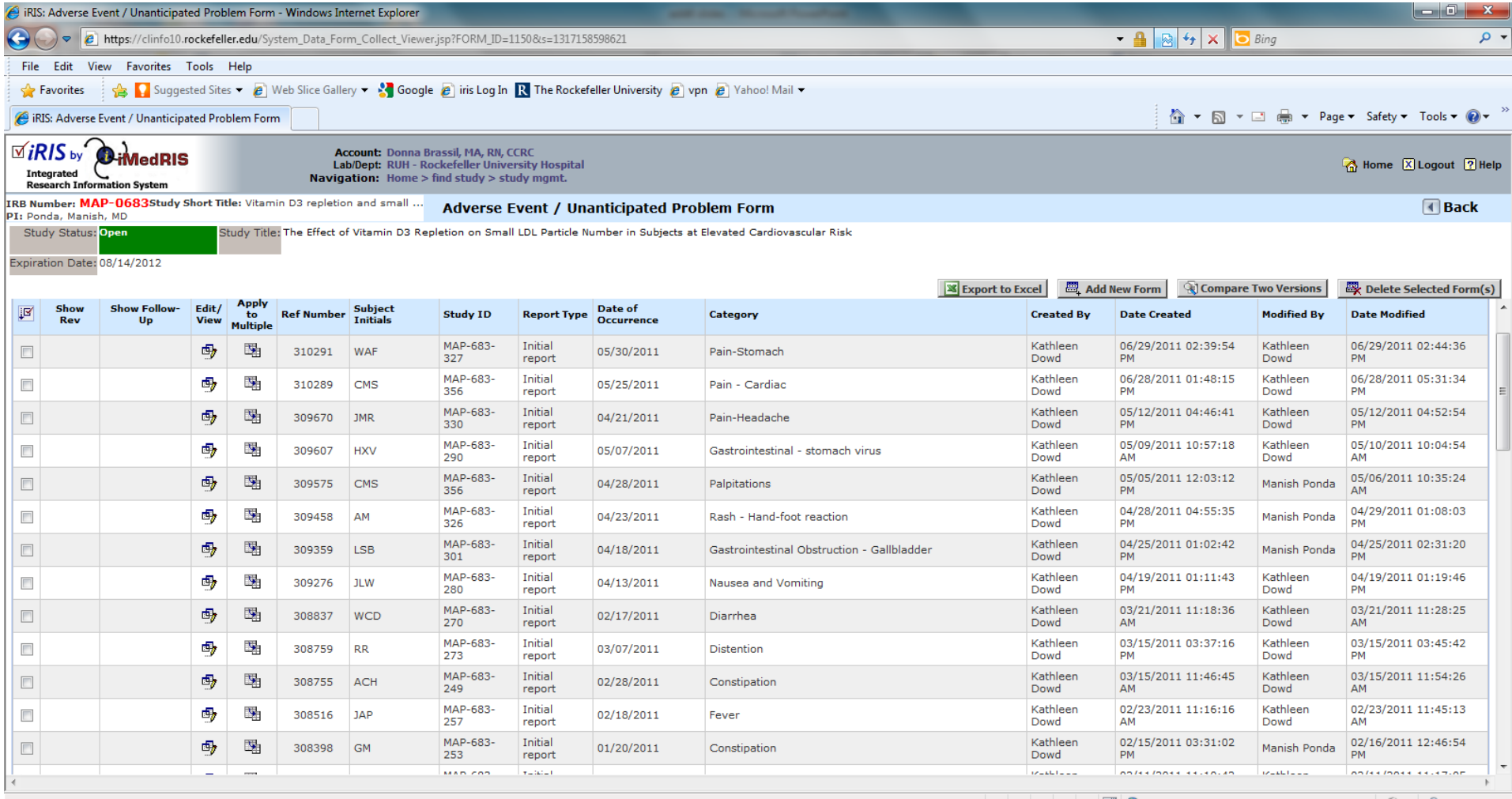
Adverse Event Log



Show Rev	Show Follow-Up	Edit/View	Apply to Multiple	Ref Number	Subject Initials	Study ID	Report Type	Date of Occurrence	Category	Created By	Date Created	Modified By	Date Modified
				310291	WAF	MAP-683-327	Initial report	05/30/2011	Pain-Stomach	Kathleen Dowd	06/29/2011 02:39:54 PM	Kathleen Dowd	06/29/2011 02:44:36 PM
				310289	CMS	MAP-683-356	Initial report	05/25/2011	Pain - Cardiac	Kathleen Dowd	06/28/2011 01:48:15 PM	Kathleen Dowd	06/28/2011 05:31:34 PM
				309670	JMR	MAP-683-330	Initial report	04/21/2011	Pain-Headache	Kathleen Dowd	05/12/2011 04:46:41 PM	Kathleen Dowd	05/12/2011 04:52:54 PM
				309607	HXV	MAP-683-290	Initial report	05/07/2011	Gastrointestinal - stomach virus	Kathleen Dowd	05/09/2011 10:57:18 AM	Kathleen Dowd	05/10/2011 10:04:54 AM
				309575	CMS	MAP-683-356	Initial report	04/28/2011	Palpitations	Kathleen Dowd	05/05/2011 12:03:12 PM	Manish Ponda	05/06/2011 10:35:24 AM
				309458	AM	MAP-683-326	Initial report	04/23/2011	Rash - Hand-foot reaction	Kathleen Dowd	04/28/2011 04:55:35 PM	Manish Ponda	04/29/2011 01:08:03 PM
				309359	LSB	MAP-683-301	Initial report	04/18/2011	Gastrointestinal Obstruction - Gallbladder	Kathleen Dowd	04/25/2011 01:02:42 PM	Manish Ponda	04/25/2011 02:31:20 PM
				309276	JLW	MAP-683-280	Initial report	04/13/2011	Nausea and Vomiting	Kathleen Dowd	04/19/2011 01:11:43 PM	Kathleen Dowd	04/19/2011 01:19:46 PM
				308837	WCD	MAP-683-270	Initial report	02/17/2011	Diarrhea	Kathleen Dowd	03/21/2011 11:18:36 AM	Kathleen Dowd	03/21/2011 11:28:25 AM
				308759	RR	MAP-683-273	Initial report	03/07/2011	Distention	Kathleen Dowd	03/15/2011 03:37:16 PM	Kathleen Dowd	03/15/2011 03:45:42 PM
				308755	ACH	MAP-683-249	Initial report	02/28/2011	Constipation	Kathleen Dowd	03/15/2011 11:46:45 AM	Kathleen Dowd	03/15/2011 11:54:26 AM
				308516	JAP	MAP-683-257	Initial report	02/18/2011	Fever	Kathleen Dowd	02/23/2011 11:16:16 AM	Kathleen Dowd	02/23/2011 11:45:13 AM
				308398	GM	MAP-683-253	Initial report	01/20/2011	Constipation	Kathleen Dowd	02/15/2011 03:31:02 PM	Manish Ponda	02/16/2011 12:46:54 PM

AE Reporting Requirements

Type of AE	Time frame for reporting to various agencies			
	IRB	Sponsor	FDA	OHRP*
AE (non serious, anticipated)	Annually	Varies	Annually	n/a
SAE	2 working days	Varies	7 working days	n/a
Unanticipated AE (if related, and > grade 2)	2 days	Varies	15 days	n/a
Unanticipated problems (other, that threaten safety, welfare, rights of participant)	5 days	Varies	"prompt reporting'; triggers off IRB report to OHRP	IRB reports to ORHP w/in 30 days of notice

* IRB reports to OHRP (not investigator)

Monitoring Adverse Events

Internal: Study Team

External: Sponsor, CRSO, FDA, OHRP

Will reconcile all chart entries and AE log

- Are all AE recognized? Documented? Tracked?
- Have reporting requirements been met?
- Are there unresolved AEs?
- Is there a pattern?
  - Expected
  - Not expected
  - What does this mean? Toxicity? Dose related?

Questions?