

# **Reportable New Information Submissions, Corrective and Preventive Action Plans, and External Reports**

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# Today's Agenda

- What is a RNI and what is reportable to the IRB via RNI
- How to prepare an RNI, guidance on the description
- Root Cause Analysis
- Crafting a **Specific, Timely, and Measurable** Corrective and Preventive Action (**CAPA**) Plan
- Examples of RNI, is this reportable? How's that description?
- University and External Reporting
- Q&A

# Recent Addition to RNI Form

## 4. \* Describe the new information:

Within the text box provided, detail the event you are submitting to the IRB, the actions taken to resolve the incident, and how this type of incident will be prevented in the future. If applicable to the event, the description must address the following:

- What happened and when?
- What factors and/or who contributed to why it happened?
- What was done to immediately address the issue?
- What is the plan going forward for preventing this from happening again?

The above bullet points were added to the RNI form to prompt more detailed descriptions and reminder to include a Corrective/Preventative action plan.

# Recent Changes to the RNI letter

- The following text has been added to the RNI determination letter:
  - External and Institutional Reporting Requirements:
  - The following determinations may require mandated reporting by the IRB to Northwestern University institutional officials and/or federal agencies such as the Office of Human Research Protections (OHRP) or the Food and Drug Administration (FDA):
    - Serious non-compliance and/or continuing non-compliance
    - Unanticipated problem involving risks to participants or others
    - Suspension of IRB approval
    - Termination of the research
- If reporting is required for this determination, the following people will receive a copy of the External or Institutional Report, which summarizes the event and subsequent action (if applicable), within 30 business days of the IRB determination date:
  - The Institutional Official,
  - School Research Dean,
  - Department Chair/Division Chief,
  - Principal Investigator, and
  - Other institutional or affiliate designees.

# NEW INFORMATION

What is a RNI? (Reportable New Information)

- Newly identified risks
- Noncompliance (with protocol/regulations/IRB policies)
- Unanticipated problems (such as a serious adverse event deemed possibly related to the research)
- Participant complaints
- Audit reports
- Sponsor suspension letters

# Definitions

**Non-compliance:** Failure to follow the federal regulations governing human research or with the requirements or determinations of the IRB.

**Serious Non-compliance:** Non-Compliance: such that the failure to comply could adversely affect the **rights, safety, or welfare** of a human subject; place a human subject at **increased risk of harm**; cause harm to a human subject; affect a human **subject's willingness** to participate in research; or **damage or compromise** the scientific **integrity of research data**.

**Continuing Non-compliance:** A pattern of Non-Compliance that suggests the likelihood that, without intervention, instances of Non-Compliance will recur, a repeated unwillingness to comply, or a persistent lack of knowledge of how to comply.

# Definitions Continued

**UPIRSO:** Any information, including any incident, experience, or outcome that meets ALL of the following conditions:

- is **unexpected** (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied;
- is **related or possibly related** to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places human subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) **than was previously known or recognized**, even if no harm has actually occurred.

# What To Include in a RNI Description?







Approach the RNI description like you're divulging juicy gossip to your best friend. We want to hear all the best parts and we might need some background information to make sense of everything.

We don't only want to know what happened, how, and why, but what will the consequences be to the parties involved and to the course of the study. Do subjects need to be notified? If so, what was their response? What other changes need to take place as a result of the new information?

# Be Transparent, Be Clear! We'll try to be too!

- When information is missing or written unclearly, the IRB will almost certainly ask for clarification, which may lead to prolonged review, and delays in implementing necessary changes or imparting new risk information.



# Guidance on Description (continued)

- Reporting Non-compliance:
  - What does the protocol mandate?
  - What deviation occurred?
  - What is the reason for the deviation?
  - What is the consequence of the deviation for the subject (if applicable)?
  - What is the corrective and preventive action that will take place as a result of the deviation/non-compliance?

# Root Cause Analysis

- For those RNI submissions involving an error or deviation, a root cause analysis is to be completed.
- A root cause analysis is not intended to lay blame on an individual
- The preventive actions in the CAPA plan cannot be formulated without identifying the cause of the error or deviation.

# Root Cause Review

- On March 28, 2019 the new project manager for the study was reviewing the records and identified that the records for participants 0278 and 0270 did not include record of payment for their first study visit. Those visits occurred on November 12, 2018 and October 15, 2018, respectively. The project manager notified the principal investigator the same day and contacted ASRSP to find out whether checks had been sent to those participants. The project manager received the response from ASRSP on April 2, 2019 that the participants were not paid. The project manager requested that ASRSP process the payments to the participants the same day.
- Root Cause: The research associate didn't process the payments for the participants.
- Corrective Actions: ASRSP confirmed the participants were sent payment via check on April 7, 2019
- Preventive Actions: The research associate who made the error is no longer at Northwestern.

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- **Root Cause: There wasn't a process in place to review participant records on an ongoing basis to ensure that all procedures were followed, as required.**
- Corrective Actions: ASRSP confirmed the participants were sent payment via check on April 7, 2019
- Preventive Actions: Beginning immediately, when participants complete study visits that require payment **processing, the research associate will place a request for payment with ASRSP and document the request in the participant record using a newly developed record sheet. The project manager will review the participant records monthly to ensure that all study procedures, including participant payments, are completed and recorded appropriately and document the review on the record sheet.**

# Corrective and Preventive Action (CAPA) Plan

- Corrective Actions: Taken to address the immediate cause of the RNI report.
  - Ex. Participant 0326 is actively participating in the study and has not reported any adverse reactions to receiving double the intended dose of study drug.
- Preventive Actions: Taken to ensure no recurrence of the cause of the RNI report.
  - Ex. On May 23, 2019 all members of the study team underwent training on the study drug dosing and implemented a new process to document dispensation of study drug. The study team member obtaining the study drug from the research pharmacy will take the participant specific study drug form to the pharmacy. The research pharmacist and the study team member will inspect the study drug bottle and study drug pills, confirm the dosage, and document their review on the study drug form.

# Corrective and Preventive Action (CAPA) Plan

- When preparing the RNI submission and writing a CAPA plan you should consider the following:
  - Is this event or deviation a recurrence, for which you already have a **CAPA** plan in place?
    - If yes, rather than writing a new preventive action plan:
      - Detail the actions that you'll take to determine why the plan failed,
      - The changes to the plan that you'll make, and
      - The ongoing assessment of the preventive action plan to determine if it is still working



# Corrective and Preventive Action (CAPA) Plan

- When preparing the RNI submission and writing a CAPA plan you should consider the following:
  - The plan should be:
    - Specific
    - Timely
    - Measurable

Ex. All members of the study team responsible for obtaining informed consent will undergo retraining by the principal investigator and project manager on how to obtain and document consent. The training will occur by October 23, 2018 with attendance recorded. The documentation of the training will be kept in the study records.

# Reportable Events

- IRB Determinations that require reporting to federal oversight/funding agencies and/or university stakeholders:
  - Serious Non-Compliance
  - Continuing Non-Compliance
  - Serious and Continuing Non-Compliance
  - Unanticipated Problems Involving Risk to Subjects or Others
  - Suspension of the Research
  - Termination of the Research

# Reportable Events

- External reports: Those sent to the federal funding agencies and/or federal oversight agencies. (NIH, FDA, DOJ, VA, etc.)
- All external reports are also reported to university and affiliate stakeholders
  - Investigator's supervisor, Department Chair, IRB Executive Director, Associate Vice President for Research, Vice President for Research, etc.
- University reports: When a study is not federally funded or under the oversight of a federal agency, the event(s) are reported to university stakeholders.

# Reportable Events

- From the date that the IRB Panel makes a reportable determination, the IRB Office Compliance Team has **30 business days** to send the report. ([HRP-094 – External Reporting Process](#))

# External IRB Studies

When the Northwestern University IRB has ceded review to an external IRB and an event occurs...

- The investigator must evaluate the event using the reporting criteria of the external IRB.
- REMEMBER: Definitions for what is reportable and the timelines for reporting differ at every IRB
- If the event is reportable to the external IRB, you must also report the event to the Northwestern IRB at the same time.

# Multi-Site IRB Studies

When the Northwestern University IRB takes on the responsibility of serving as the IRB of record for external sites, you have a new role...

- Study Coordinating Center
  - Your responsibility is to ensure that the other study teams are evaluating events according to the Northwestern IRB reporting criteria; and
  - Facilitating the RNI submission in the eIRB+ system and communication between the site and the NU IRB

# Scenario 1

- On 4/3/2017 a participant that was scheduled to receive a tracer dose for a PET scan received a dose that had an activity level of 4.1 mCi. Our protocol states that our dose range should be 5-6 mCi. This occurred because our radiopharmaceutical partner was late with their delivery of the dose to Northwestern Memorial. The dose was calibrated to be injected at 12 pm with an arrival time slated prior to that. However the dose did not arrive until 12:30 pm which placed us behind the pre-determined schedule. Moving forward, we'll be reaching out to our partner and working with them to resolve delivery issues and delays so we can ensure our doses are arriving at the pre-scheduled time.
- -Is this reportable? Why or Why Not?
- -What information is missing?

## Scenario 2

- Staff became aware that a participant was dispensed an incorrect, lower dosage of medication. After consulting with the study doctor, staff instructed the participant via telephone to take 2 pills 3 times per day instead of 1 pill 3 times per day in order to receive the correct amount of medication until the following visit. Per pill count, the participant took the appropriate dose of study medication until returning the following day to receive the correct prescription. No adverse events were reported by the participant. The patient took the incorrect dose for 24 hours (1 day).
- A data entry error from an internal spreadsheet was found to be the cause for the prescription to be ordered at a lower dose when the participant had already titrated up to a higher dose. CAP: Staff will no longer use an internal spreadsheet to mark titration levels of medication for patients. At medication visits, staff enter prescription numbers and titration levels in REDCap while prescription is in front of them. Going forward, staff will check these prior to visits in REDCap before ordering prescriptions from the pharmacy.



## Scenario 3:

When conducting an interview with one of the faculty members, they noticed that the form said "You are being asked to take part in this research study because you have TAKEN a content-based or language for specific purposes course on campus." instead of "You are being asked to take part in this research study because you have TAUGHT a content-based or language for specific purposes course on campus." Basically the student criteria was included on the faculty consent form as well. I remedied it with the faculty member and made the correction. This honest mistake affected 2 people. One faculty member noticed the error and I corrected it on the form and she signed it, another faculty member did not notice the error and signed the form. I plan to resubmit a modification and upload the new consent form as well as re-email the 2 faculty members the correct consent form and follow the same protocol that provides them the opportunity to ask any questions or for any clarifications.

## Scenario 4

A recently completed related trial, a randomized controlled trial of a breathing monitoring/regulating device versus usual care in heart failure patients with EF < 45% and predominant central sleep apnea, was completed and the data was analyzed. The findings revealed that the primary endpoint was neutral, however, there was an adverse signal regarding total mortality, and specifically cardiovascular mortality with a statistically significant increase in cardiovascular mortality. The company has now issued a contraindication in patients with EF < 45%, thus the patients in the current study meeting this criteria on the study arm will need to be discontinued from the study therapy. Patients are being asked to stop using the study device, but continue the protocol as planned, and return their device on the next scheduled visit. Sponsor's revisions to protocol and ICF are forthcoming. Once received, we will submit with patient notification letter. Note: patients have already been contacted by the PI.



# Ultimately, We're Here to Help

