What’s New?
RSPP SOPs
Research Subject Protection Program
Three new/revised RSPP SOPs are being released – with implementation/effective date of 12/15/17

- SOP 403: Changes to Approved Research
- SOP 601: Noncompliance in Human Subject Research
- SOP 410: Reporting & Review of Unanticipated Problems in Human Subject Research
WHY?

- Federal regulations require prompt report of incidences of Serious/Continuing Noncompliance (NC) – the RSPP current process requires the PI to make the initial determination of significant vs. minor violation. If incorrectly categorized, the reporting of minor violations /NC at Continuing Review is not prompt reporting.

- Assist in determination of Continuing NC – eventual shift to submission of NC using RedCap – will allow for generation of reports
WHY?

- Create a process for broader reporting of Unanticipated Problems per AAHRPP standards – “funnel concept” – discussed later in presentation.
- Per SACHRP recommendation (based upon FDA/OHRP statements), intentional protocol deviations are changes in approved research; deviations without prior approval are noncompliance.
- Attempt to simplify the RSPP SOPs and definitions and streamline the review process – especially noncompliance.
- Put SOPs Aurora system policy format.
The current version of RSPP SOP 403 has undergone major revision – including title change.

What’s included in new SOP…

– What constitutes a Change in Approved Research
– How to report a Change in Approved Research
Changes in approved research include modifications, additions or deletions to the study or study plans/ processes that were reviewed and approved by the IRB or require IRB review and approval.
A Change to Approved Research also includes Protocol Exceptions:

- Must obtain **prior sponsor approval** before submission of Change to the Aurora IRB
- IRB approval is required **before** the change is implemented. Otherwise the change will be considered noncompliance.
- Use Change form to request of IRB
- No longer need to single out Protocol Exceptions at Continuing Review
What’s different?

– **Changes** are considered effective on the date of IRB approval and should be implemented as soon as possible but no later than 30 days after receipt of communication from the RSPP Office. Delays in implementation beyond 30 days must be reported to RSPP. This will then be reviewed as Noncompliance.

– Added at request of some research teams.

It will be your responsibility to track the implementation date of changes. If you do not meet the 30 day implementation timeframe, you WILL need to report this to the RSPP.
What’s different?

- **Changes** that are made to eliminate apparent immediate hazard to subjects and occur at a site for which Aurora’s IRB has oversight should, whenever possible, be reported to RSPP within 5 working days of initiation of the Change.

**Changes** that are made to eliminate apparent immediate hazard to subjects are reported to the IRB using the Unanticipated Problem Reporting form/process. These changes, although intentional and contrary to the approved protocol, are not considered Noncompliance.
What about the parts of current SOP 403 that have been removed by SOP revision?

– Administrative holds
  • Added to RSPP SOP 407: Administrative Hold, Suspension Or Termination Of IRB Approval

– Subject complaints
  • Those that are not reportable as UPs may be reported at Continuing Review.

– Significant New Findings
  • New SOP and form being generated
Changes to Approved Research Reporting Form (form 403)

- New title to match the SOP
- Has undergone revision
  - Check boxes for ease of submission
  - Eliminates PI signature – unless new PI is being added to study
SOP 601: Noncompliance

The current version of RSPP SOP 601 has undergone major revision. The new SOP applies to both studies that are ceded to an external IRB or studies under Aurora IRB oversight.
What’s included in new SOP...

- New definitions of noncompliance
- Examples of what constitutes noncompliance
- How to report noncompliance by an investigator or key research personnel

Note that Noncompliance does not include failure by the subject to follow the protocol or investigator/study team instructions, that is, Subject Noncompliance. Subject Noncompliance does not need to be reported – unless it meets the Unanticipated Problem reporting criteria.
Noncompliance means:
Failure (intentional or unintentional) of an Investigator, his/her designees, IRB members, RSPP staff members, or others involved in the conduct or review of research involving human subjects to adhere to:

a) federal, state or local human subject protection laws, regulations, or policies;

b) Aurora system policy Research Involving Humans or Their Identifiable Specimens;

c) Aurora Research Subject Protection Program (RSPP) standard operating procedures governing the review and conduct of human subject research;

d) IRB determination; and/or

e) IRB-approved protocols, excluding changes made to eliminate apparent immediate hazard to subjects
Serious Noncompliance means:

Noncompliance that in the judgement of the reviewer or reviewing body, as applicable, has been determined to:

(a) result in hospitalization or an irreversible, long-term, life-threatening or fatal medical occurrence, or require medical or surgical intervention to prevent one of these outcomes;

(b) Significantly increase the potential risk of harm to study subjects should the noncompliance recur;

(c) Significantly compromise subject rights; or

(d) Significantly impact the integrity of the study/data.
Continuing Noncompliance means:

Noncompliance ( Serious or non-serious ) that continues to occur despite previous identification of the problem and subsequent corrective and preventive action, and which the reviewer or reviewing body, as applicable, has determined that, if allowed to continue, is likely to adversely affect the rights, welfare and/or safety of research subjects or adversely affect the scientific integrity of the study/data.

Also includes situations where the same type of noncompliance event occurs by the same research staff/PIs but in different studies.
SOP 601: Noncompliance

What is to be reported?

– Investigators/research teams are required to report anything that meets the definition of noncompliance, in studies overseen by the Aurora IRB or ceded to an external IRB.

When is Noncompliance to be reported?

– Anything that meets the definition of noncompliance per SOP 601 should be reported as soon as possible, but in no case later than 10 working days from the date of discovery.
What’s different?

– There is no longer a distinction between types of violations (e.g. minor vs. significant). “Violation” is no longer part of the IRB’s vocabulary.

– All noncompliance, as defined by SOP 601, is to be reported within 10 working days of discovery.

– **Subject noncompliance** does **NOT** meet the definition of noncompliance per SOP 601 and does not need to be reported as such.

Subject noncompliance must be considered under the Unanticipated Problem SOP to determine whether it should be reported as a UP.
What does this mean?

– As of 12/15/17, all noncompliance must be submitted in real time.

– For those studies in the midst of a continuing review cycle, you may submit minor violations discovered until 12/15/17 on the violation spreadsheet. However, after the implementation date, all noncompliance must be submitted in real time. If not, this will be considered noncompliance.

– The violation spreadsheet will no longer be accepted after 12/2018.
Noncompliance examples include:

- Failure to obtain IRB approval prior to any protocol change
- Failure to follow protocol (e.g., out of window visits, dosing error, lab processing error, inclusion/exclusion criteria error, etc.) except for those caused by study subjects (e.g., subject refused follow-up appointment, subject failed to take prescribed drug despite instructions, etc.) or changes made to eliminate apparent immediate hazards to study subjects
- Failure to obtain or document informed consent or failure to use the IRB approved consent form or other material
- Failure to obtain IRB approval for human subject research
- Failure to follow Aurora system policies on human subject research or RSPP/Aurora IRB SOPs
- Failure to follow study-specific IRB directives
Noncompliance Reporting Form

- **New**: Investigator Noncompliance Reporting Form (Form 601)
- You must include the action taken to **correct** the issue of Noncompliance, as well as the action that will be put into place to **prevent** the Noncompliance from recurring.

Note that there is no longer a requirement for the PI to sign the reporting form. The submitter must attest that the PI has been made aware of the Noncompliance report.
SOP 410: Reporting & Review of Unanticipated Problems in Human Subject Research (NEW)

What’s included in new SOP…

– Criteria for what constitutes an Unanticipated Problem (UP) / Unanticipated Problem Involving Risks to Subjects or Others (UPIRIRSO)
– Difference between a local and external UP
– How to report an Unanticipated Problem Involving Risks to Subjects or Others (UPIRIRSO)
New UP definition – any incident, experience or outcome that is:

• unexpected in terms of its nature, severity or frequency given the research procedures that are described in study documents submitted to the IRB (e.g., protocol, consent form, investigator’s brochure, etc.) and the characteristics of the Subject population being studied;

• regarded as unwelcome or harmful and something that may need to be dealt with or overcome; and

• is related or possibly related to the research.
Old definition – UP is an event that meets **all** of the following criteria:

• Is more likely than not related to the research [“related or possibly related”];

• Negatively affects the risk/benefit ratio of the research (this includes physical, financial, confidentiality as well as psychosocial risks); AND

• Was not described in the protocol, Investigator's Brochure, IRB application, or informed consent document OR exceeds the specificity, frequency, or severity described in these documents [“unexpected”].
UPIRSO is defined as:

a UP that the IRB Chair/designee determines involves a **new or increased risk** to Subjects or Others (including physical, psychological, economic or social) that either:

- might affect Subjects’ willingness to continue participation, **OR**
- requires some action e.g., modification of the consent process, informing participants, modifying the study protocol or procedures, etc.
For studies that are overseen by the Aurora IRB, PIs must promptly inform the RSPP Office of:

- Local UPs that, in the judgement of the local PI or study sponsor, are determined to more likely than not meet the definition of an UPIRSO

- External UPs that the sponsor or lead PI of a multi-center trial has determined meet the definition of an UPIRSO
UPs
---
Reportable UPs
---
IRB Decision
---
UPRISOS

- Changes w/o Prior Approval
- Subject Noncompliance
- Privacy Breaches
- Subject Complaints

- Unexpected;
- Related/possibly related; and
- Unwelcome/harmful & requiring action?

- Sponsor deemed UPIRISO?
- PI determines > chance than not UPIRISO?

- New/increased risk?
- Affects participation/requires action?
For studies that are overseen by an external IRB:

• You must follow the IRB of Record’s reporting requirements.

• If you report a UP to the IRB of Record, you must immediately provide a copy of that notification to the Aurora RSPP per SOP 409.
What does promptly mean?

UPs must be reported within 5 days of discovery regardless of whether they occur during the study, after study completion, or after participant withdrawal or completion.
What’s different?

After 12/15/17…

– The Aurora IRB will **NO LONGER ACCEPT** local or external AEs/UPs that are not reportable Unanticipated Problems under SOP 403.

– The Unanticipated Problem Reporting Spreadsheet will no longer be accepted at Continuing Review.

– SOP 410 has a policy statement that can be shared with the sponsor addressing this change.
UP Examples include:

- Complaints from subject or others
- Breach of privacy or confidentiality
- Changes made to research without prior approval in order to eliminate apparent immediate harm
- An unintentional change in the study plan for an individual Subject or series of Subjects
- Subject noncompliance (e.g., missed dosing, refused appointment)
- Significant New Findings
- Adverse Event/device effect
- Events determined by a sponsor or multi-center lead PI to be meet the definition of a UPIRSO

Put events through the UP “funnel”. Report only those events that meet SOP criteria.
UP Reporting Form

- **New**: Unanticipated Problem Reporting Form (Form 410)
- Must include the action taken to address the UP, as well as the action that will be put into place to prevent the UP from recurring.

Note that there is no longer a requirement for the PI to sign the reporting form. The submitter must attest that the PI has been made aware of the UP report.
Case 1

A protocol-required lab test was not run for subject, John Smith, because Mr. Smith was in a hurry and refused to stay for the test. The purpose of the lab test was to collect additional data only—not for safety reasons.

- Is this reportable to the IRB?
  - Why or why not?
  - If yes, in what timeframe?

- How would your answers change if the test was not run because the investigator deemed it not necessary—Mr. Smith was willing to have the test?
Case 2

An Investigator is concerned about administering a protocol-required dose increase at the subject’s next visit. The subject called into the office to report an adverse reaction and it was managed over the phone, but the subject’s next visit at which the dose increase is supposed to occur is only five days from now. The protocol does not allow for a hold on dosing because of this adverse reaction. The investigator asks your advice on whether he should discuss or report his intent to not increase this subject’s dose to the IRB.

• How do you respond? Should this be reported to the IRB?
  – Why or why not?
  – If yes, in what timeframe?
• How would your answers change if the investigator did not ask your advice but instead went ahead and held the subject at the same dose because of concerns over subject safety?
Case 3

Twelve study subjects at four different institutions participating in the study have experienced seizures while on study drug. Seizures were not a previously known risk of study drug and were not included in the informed consent document. Seizures are not common in this study population, but are also not unheard of. Aurora subjects have not experienced any seizures to date. The sponsor does not believe the occurrence of the seizures meets the definition of an unanticipated problem involving risks to subjects or others.

• Is this reportable to the IRB?
  – Why or why not?
  – If yes, in what timeframe?

• How would your answers change if one or several Aurora subjects also experienced seizures and the local PI felt the seizures represented an unanticipated problem (UP) that was more likely than not to meet the definition of a UP involving risks to subjects or others?
Key Points - SOP 403 Changes to Previously Approved Research

- SOP 403 has undergone major revisions including a title change
- Form 403 has undergone revisions including title change
- All protocol exceptions should be requested on Form 403
- The protocol exception continuing review reporting grid and flowchart are being retired.
- Protocol exceptions approved/acknowledged by the Aurora RSPP do not require re-reporting at continuing review
- Changes made by the site to eliminate apparent immediate hazard to subject(s) should be reported to the Aurora RSPP within 5 days on the UP Form 410
- Changes made to approved research that may impact subject safety or the risk/benefit analysis should be submitted to the Aurora RSPP within 30 days. All other changes made to approved research should be submitted within 90 days.
- Changes approved by the Aurora RSPP are effective on the date of IRB approval and should be implemented as soon as possible but no later than 30 days after receipt of approval from the Aurora RSPP.
- Changes that cannot be implemented within 30 days of receipt of Aurora RSPP approval should be reported to the Aurora RSPP via email, prior to the end of the 30 day period.
Key Points - SOP 601 Non-compliance

- Definition of non-compliance has changed
- Non-compliance definition excludes subject non-compliance, which now is reported only if it meets the definition of an unanticipated problem (UP)
- The term "violation" is no longer used and has been replaced by/is considered non-compliance
- All non-compliance, minor or significant, is reported real-time for all studies, regardless of whether overseen by local or external IRB
- Report all non-compliance within 10 days
- Non-compliance (formerly violations) are no longer summarized and reported at continuing review
- Use the new Investigator Non-Compliance Reporting Form (Form 601)
- Investigator does not need to sign the Form 601 but submitter must attest PI is aware of the non-compliance
- Non-compliance that occurs on or after 12-15-17 must be reported on the Form 601.
- Non-compliance (violations) that occurred prior to 12-15-17 can remain on the current violation reporting grid for reporting at time of continuing review
The definition of unanticipated problem has changed slightly. The investigator must still evaluate incidents, events, and outcomes and decide if they meet the definition of UP AND most likely an unanticipated problem involving risks to subjects or others (UPIRSO). The IRB chair/designee determines if the reported incident, event, or outcome is indeed a UPIRSO. UPs are reported on a new Unanticipated Problem Form (Form 410). UPs must be reported to the Aurora RSPP within 5 days. Internal/external adverse events (Medwatch/CIOMS/IND safety reports) that are not UPs/UPIRSOs are not reported/accepted by the Aurora RSPP. A statement to this effect is included in the revised SOP – may be shared with the sponsor. Investigator does not need to sign the Form 410 but submitter must attest PI is aware of the UP/UPIRSO. Studies ceded to an external IRB continue to follow the reporting policies of that external IRB, however; a copy of any local UPs/UPIRSOs submitted to an external IRB should be sent to the Aurora RSPP at the same time reported to the external IRB per Aurora RSPP SOP 409.