Process for Identifying Adverse Events Among Resident Physicians in Participating Programs

The iCOMPARE study has an independent, NHLBI-appointed Data and Safety Monitoring Board (DSMB) operating under a Data and Safety Monitoring Plan (DSMP). Relevant sections of the DSMP read as follows:

Collection of Serious Adverse Events and Unanticipated Problems

NHLBI defines a Serious Adverse Event (SAE) as:

> An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

In iCOMPARE, the following events will be considered SAEs: death or hospitalization of an intern, removal of an intern from their schedule or rotation because of mental of physical condition potentially related to their duty hours, motor vehicle accident in which the intern was the driver, needle stick experienced by intern, and other on the job injury to intern.

NHLBI defines unexpected events as those that are "not consistent with the risk information described in the general investigational plan or elsewhere in the current application". The events considered SAEs in iCOMPARE are not unexpected inside of iCOMPARE but similarly they are not unexpected outside of iCOMPARE. For each SAE listed above, we expect training programs randomized in iCOMPARE to have similar event rates regardless of duty hour schedule assignment.

We will ask each program director to provide a narrative report of occurrence of any of the events listed above. The catchment will be by self-report; program directors will be queried periodically about event occurrence and reminded to provide these reports. The DCC will abstract information to provide counts and to calculate rates of occurrence.

NHLBI defines suspected events as those for which "there is a reasonable possibility that the drug caused the adverse event". In iCOMPARE, this definition will be modified so that suspected events are those for which there is a reasonable possibility that the *intervention* caused the adverse event. The Steering Committee will classify events as 'suspected' based on subjective assessment of the details included in the narrative provided by the internal medicine program director.

The Office for Human Research Protections (OHRP) defines an unanticipated problem as "any incident, experience, or outcome that meets all of the following criteria: 1) unexpected; 2) related or possibly related to participation in the research; and 3) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized". Since these are, by definition, unanticipated, it is impossible to state, a priori, what kind of unanticipated problems we expect in iCOMPARE. However, unanticipated problems in iCOMPARE might include differential rates across treatment groups of intern fatigue-related accidents, near misses or injuries; breaches of protocol in duty hour scheduling that result in trainees working more than the intervention schedule dictates; or breaches of intern or patient confidentiality.

iCOMPARE will rely on self reporting by program directors regarding SAEs and unanticipated problems. A reminder to report these occurrences will be included in the periodic updates provided to program

directors and on meeting agendas.

Monitoring procedures
Steering Committee monitoring of safety and performance data

Frequency: The Steering Committee will monitor accumulating safety and performance data at least quarterly to help assure participant safety and for quality assurance.

Internal medicine residency programs are typically three years long and so at any one time include residents in their first, second, and third years of training. Under current duty hour rules, second and third year internal medicine residents are already permitted to work shifts of up to 28 hours in length. First year residents under current rules established in 2011 typically work shifts no longer than 16 hours, although in their second and third years they will work shift lengths of up to 28 hours. Therefore, the intervention of the iCOMPARE trial effectively allows first year residents to work shift lengths that they could work in their second and third year. Safety monitoring of residents in iCOMPARE is only for interns (residents in their first year) because the flexibility introduced by the iCOMPARE intervention predominantly changes rules affecting first-year residents.

Surveillance of work-related problems in internal medicine residency programs under normal circumstances falls to the directors of those residency programs and it is those usual mechanisms that are employed in the iCOMPARE trial. All program directors, regardless of the assignment of their program to intervention or control, are periodically reminded to report any adverse events through a number of mechanisms, including as part of regular emails and discussion at meetings. The most recent reminder was sent on December 1, 2015, and reads as follows:

From: Kelsey Gangemi [mailto:kgangemi@mail.med.upenn.edu]
Sent: Tuesday, December 01, 2015 10:25 AM
To: XXX
Cc: Asch, David; 'Sanjay Desai'; Judy Shea
Subject:iCOMPARE Adverse Event Reporting Reminder

Dear iCOMPARE PDs,

As a reminder, it extremely important for you to alert the iCOMPARE study team **as soon as possible** if an adverse event or unanticipated problem occurs with an intern in your program. **It is critical that *both* FLEX and CURR programs report the specified events—this will enable us to accurately compare event rates between groups.**

For the purposes of this trial, we ask that you report to us the following serious adverse events and unanticipated problems:

- Serious adverse events
  - Death or hospitalization of an intern
  - Removal of an intern from their schedule or rotation because of a mental or physical condition potentially related to their duty hours
  - Motor vehicle accident when the intern was the driver
  - Needle stick experienced by intern
- Unanticipated problems

- Any unexpected event you assess as being related to participation in the trial that places an intern at greater risk of harm than expected

When reporting an event, please provide the following information:

- Event date
- Descriptive narrative detailing the event, including the kind of rotation the interns were on at the time.

NOTE: Please do not provide the name of the intern. However, if name is provided, we will redact the intern's name before the report is forwarded for review by the study entities listed below.
Please send this information directly to Kelsey Gangemi at kgangemi@mail.med.upenn.edu or call at 215-746-8438. Reports will be reviewed by numerous study related entities including the trial Directors, the iCOMPARE Data and Safety Monitoring Board and the iCOMPARE Steering Committee.
As a reminder, this is an essential component of the trial and we will prompt for this information regularly to ensure the safety of our trainees.

Please let us know now if you have experienced any events above since July 1st.

Many thanks,
The iCOMPARE team

Follow up messages like the one above include the request to submit events since the start of the study, in case older events come to light later. Events involving interns reported to iCOMPARE by this mechanism are stripped of the identifying program information and submitted to three internal medicine physicians on the iCOMPARE steering committee for a preliminary assessment of study connection and report completeness. All received reports (regardless of study connection attribution) are forwarded to the Data Coordinating Center (DCC) with the program information reattached. DCC personnel compile the reports and send them weekly to the DSMB Executive Secretary at NHLBI who forwards them to the DSMB chair and the medical monitor for independent and immediate review. An experienced internal medicine physician/residency program director member of the DSMB is designated as the medical monitor and is charged with adjudicating whether these events are study related, whether more information is needed about the circumstances or resolution of the event, and whether the event needs further review by the full DSMB. The full DSMB receives the accumulated reports quarterly.