iCOMPARE Data and Safety Monitoring Plan

06 October 2015

Monitoring overview

iCOMPARE data and safety will be monitored by the Steering Committee and by an independent Data and Safety Monitoring Board (DSMB) as required by NIH guidelines for multicenter trials. The Steering Committee and the DSMB will monitor accumulating safety and performance data. No interim analyses are planned because the intervention phase will be completed before patient mortality data are available. Many of the education outcomes also will not be available until after completion of the intervention phase. However, during the intervention phase, the DSMB may monitor performance data, sleep and alertness outcomes, time and motion outcomes (as available), and reports of safety concerns relating to trainees, faculty or patients as provided by program directors or otherwise brought to the attention of the iCOMPARE investigators. The DSMB is a multidisciplinary group with a written charge, with members appointed by NHLBI. The DSMB will be advisory to the NHLBI.

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.

Content: During the implementation stage of the trial, the Steering Committee will monitor the 1) timeline and progress of refinement of the protocol and other study documents; 2) enrollment of programs; 3) attainment of IRB approval at each participating site; and 4) survey and database development. As data collection begins, the Steering Committee will begin to monitor progress of 1) completion of surveys by trainees and faculty; 2) harvesting of data on the intern sleep and alertness measures; 3) harvesting of data from time and motion observation sessions; 4) data requests and receipts from the ACGME, ACP, and APDIM for education measures; 5) data requests and receipts from Medicare; 6) compliance with the assigned duty hour schedule; and 7) reports of safety concerns. Reports of safety concerns (see previous section for definitions and data collection) may be received by the CCC or DCC directly from site staff or as noted by investigators upon review of performance data reports; reports of concerns will be reviewed by the CCC and DCC directors upon receipt and will be reviewed by the Steering Committee in a timely fashion.

Report creation: The DCC will be responsible for the production of the reports for review by the Steering Committee. The reports reviewed by the Steering Committee will include performance data and safety data, but will not include treatment effects data. Since the Flex and Curr assignments are unmasked, where feasible, data presented by site will be presented with the site's name masked.

DSMB monitoring of safety, performance, and treatment effects data.

Frequency: Because the NIH grant began on 12 August 2015, the DSMB will not review the protocol for the iCOMPARE trial before the interventions begin, but will review the protocol prior to the start of the substudies. The DSMB will meet after NHLBI funding begins and every 6

months thereafter (or as needed) to review available safety, performance and treatment effects data. The DSMB will review the data described above that is prepared for Steering Committee review; however, the DSMB will also review unmasked data by treatment group. The DSMB may request more frequent meetings to review issues that arise during conduct of the trial.

Content: The content of the DSMB reports will be drafted by the DCC and presented for input to the DSMB members and NHLBI representatives. The DSMB will review the iCOMPARE DSMB charter, protocol, consents, and data and safety monitoring plan shortly after funding begins. The DSMB will monitor the accumulating performance data (e.g., survey return rates, completeness of data acquired from outside sources) by program and treatment group. The actigraphy data on sleep/wake time and measures of intern alertness, the time and motion measures, trainee survey data on work intensity and work and education activities, and trainee and faculty survey data on satisfaction and perceptions will be accumulating during the intervention period and will be included in DSMB reports as available. Reports on the progress of obtaining education data from ACGME, APDIM and ACP will be included. Reports may include data tables, graphs, and figures.

De-identified narrative reports of SAEs and unanticipated problems (i.e., serious, potentially fatigue-related events, such as death, hospitalization, accident, near miss or injury; see section above for more details) will be included in reports. Event counts and rates will be presented, by treatment group.

The patient safety outcomes (mortality, length of stay, complications, readmissions) are generated from Medicare claims data, and each calendar year of claims data is generally available 9 months after the end of the relevant calendar year. Because of this delay, no report to the DSMB during the intervention phase will contain data on the primary outcome and other patient safety outcomes derived from Medicare claims data and there are no statistical data monitoring guidelines for early stopping of the trial. The Medicare data for the first six months of the intervention year (7/1/2015 –12/31/2015) are expected to be initially released by CMS in the fall of 2016 (final release is expected in January 2017). At a DSMB meeting scheduled early in 2017 the DSMB could get a preliminary look at the primary outcome results for the first six months of the intervention, although the intervention will be completed by the time the report is prepared. The Medicare data for the second six months of the intervention year (1/1/2016-6/30/2016) are expected to be initially released by CMS in the fall of 2017.

The DSMB will review the progress of manuscript preparations. The DSMB will review the draft manuscript reporting the primary outcome prior to journal submission.

Report creation: The DCC will be responsible for preparing reports for the DSMB to review. While data collection is ongoing, the DSMB report will include information on data acquisition and quality and other performance measures, using the most recent information available at the time the report was prepared. The DCC will prepare unmasked reports for the DSMB.

Identification and circulation of external evidence (e.g. from other trials/systematic reviews) will be the responsibility of the director of the CCC and will be presented to the DSMB if applicable, along with assessment of any impact of the new evidence on operations and continuation of iCOMPARE. One charge to the Advisory Board assembled for this project is to assist in the identification of external evidence. Any DSMB member may also bring pertinent information to a DSMB meeting.

The report will be sent to DSMB members at least one week before any meetings. The DSMB

charter will document the meeting organization and DSMB voting rules. We expect the DSMB meetings will be a mix of in person and conference call meetings, depending on the content to be covered; the DSMB will decide the mode for each meeting.

Data analysis plans and interim stopping rules

The data analysis plans for the primary and secondary outcomes are described in the iCOMPARE protocol. We do not expect to have formal interim looks or stopping rules for the primary or secondary outcomes due to design and data delay issues discussed above.

Reporting Mechanisms

The Common Rule requires written procedures and policies for ensuring reporting of adverse events and "unanticipated problems" involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head. Definitions and data collection of serious adverse events and unanticipated problems are described above. Serious adverse events that are fatal or life-threatening, unexpected, and suspected to be caused by the intervention will be reported to the overseeing IRB, NHLBI and DSMB chair or other individual designated by the Chair to complete these safety reviews within 7 calendar days of initial receipt of information. Other SAEs that are unexpected and suspected will be reported to overseeing IRBs, the DSMB, and NHLBI within 15 calendar days of initial receipt of information. All SAEs will be reported to IRBs in annual reports and to the DSMB during regular meetings.

In iCOMPARE, unanticipated problems involving risks to participants or breaches of protocol which might entail risk to participants will be reported to the University of Pennsylvania IRB (Penn IRB) or the relevant program IRB, the NHLBI and DSMB chair within the required timelines (2 weeks for unanticipated problems that are not SAEs). The Penn IRB is serving as a central IRB for iCOMPARE for the sites and programs whose IRBs agree to defer to the Penn IRB for review of iCOMPARE. The DSMB will provide the DCC with guidance regarding whether events should be reported in real time to all DSMB members (versus reporting to Chair in real time and other members at the next meeting) and what timeline for response should be mandated. At minimum, the full DSMB will review all unanticipated problems during regularly scheduled meetings and can request more frequent reports.

The DSMB response to suspected and unexpected SAEs and to unanticipated problems will be recorded by the DCC. Any further action for the programs or information needed from the programs will be communicated to Program Directors by the CCC.

The CCC will submit protocol or consent form amendments to the Penn IRB and to each site not using the Penn IRB for submission to their local IRB. The CCC will collect data on current IRB approvals and actions and will transmit this information to the DCC for inclusion in the DSMB report for review at regularly scheduled meetings.

NHLBI will provide investigators with a summary report after each DSMB meeting, with recommendations for the trial. The CCC will forward these recommendations to the IRB of record and program directors for submission to other IRBs.

iCOMPARE is not subject to FDA review or reporting.

Procedures for minimizing research-associated risk and protecting confidentiality of participant data

Risks to patients: iCOMPARE has no systematic procedures for protecting patients from risks of the duty hour schedule, aside from the self-report by program directors of adverse events

such as described above. De-identified Medicare claims data are used to analyze patient mortality and other clinical outcomes; this approach minimizes risk of breach of patient confidentiality and is judged to be the least intrusive method of measuring patient safety outcomes.

Risks to trainees, faculty and program directors: iCOMPARE will collect survey responses and educational assessment scores that are individually de-identified and so should present little to no risk to confidentiality. For faculty, iCOMPARE will collect survey responses that are individually de-identified and so should present little to no risk to confidentiality. All program directors will communicate to their trainees that participation in the iCOMPARE surveys will have no effect on their assignments or evaluations. All program directors will communicate to their faculty that participation in the iCOMPARE surveys will have no effect on their status as program faculty. Program directors will not know the survey completion status or responses of individual trainees or faculty.

To mitigate risks of fatigue, all trainees received structured education in sleep deprivation and fatigue management at the start of the intervention year.

Trainees who enroll in the Sleep and Alertness Substudy will provide written informed consent to their participation and will be assigned an ID number by which their data will be identified; only the staff member who enrolls the trainee will be able to connect the trainee's name with the ID number used with their actigraphy data and measures collected by smartphone. Trainees have the option of removing the actigraph and not responding to the smartphone assessments at any time during the 14 days of data collection.

Trainees who enroll in the Time and Motion Substudy will provide written informed consent to their participation and will be assigned an ID number by which their data will be identified; only the staff member who enrolls the trainee and the observer who observes the trainee will be able to connect the trainee's name with the ID number used with their observation data. Trainees have the option of asking the observer to cease data collection at any time.

All portions of the iCOMPARE data system will be password protected using a standard challenge/response system coupled with a user-specific identity system requiring users to log in with their personal PIN and password, which are checked before the login is completed. Once the user is logged in, all activities are stamped with the user's PIN and date-time stamp.

Knowledge of trainee and faculty names and email addresses will be limited to staff who need to know that information.

Benefits to patients, trainees, faculty and program directors

There may be no direct benefits to patients. The trainees, faculty and program directors in the Flex programs may benefit from the more flexible scheduling option.