individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE) Data and Safety Monitoring Board (DSMB) Teleconference Minutes, October 13, 2015

DSMB Members Present: O. Dale Williams, MPH, Ph.D., Chair; Gregory Belenky, M.D., FAPA; George Howard, Dr.PH.; Lia Logio, M.D.; Denise Rousseau, Ph.D.

DSMB Members Absent: Laurie Zoloth, Ph.D.

Clinical Coordinating Center (CCC): David Asch, M.D.; Mathias Basner, M.D., Ph.D.; Sanjay Desai, M.D.; David Dinges, Ph.D.; Judy Shea, Ph.D.; Orit Even-Shoshan, M.D.; Kelsey Gangemi, MPH; Michael Trentalange

Data Coordinating Center (DCC): James Tonascia, Ph.D.; Lea Drye, Ph.D.; David Shade, J.D.; Jeffrey Silber, M.D., Ph.D.; Alice Sternberg, ScM

NHLBI Staff: Carol Blaisdell, M.D., Executive Secretary; Peyvand Ghofrani, MDE, CCRA, Clinical Trials Specialist; Lora Reineck, M.D., Project Officer; Colin Wu, Ph.D., Statistician

INTRODUCTION

- The first meeting of the iCOMPARE DSMB was called to order at 2pm.
- Participants on the call introduced themselves.
- The Executive Secretary explained the charge to the DSMB and expressed the importance of the DSMB's role in oversight of all portions of iCOMPARE including the parent study (funded by ACGME) and the sub-studies (funded by NHLBI).
- The Executive Secretary reminded the participants of the confidentiality of the discussion and meeting materials and each member confirmed that there were no new conflicts of interest with service on the DSMB and reaffirmed confidentiality. DSMB members specifically confirmed no conflicts of interest with ACGME and FMCSA which provide funding and supplies for iCOMPARE.

Open Session (DSMB Members, CCC and DCC, NHLBI Staff):

The purpose of the first iCOMPARE DSMB meeting was to review the parent study and the sub-studies, including the protocol, consent, DSMB charter, data and safety monitoring plan, and statistical analysis plan.

iCOMPARE is a cluster randomized trial involving 63 ACGME accredited Internal Medicine residency training programs randomized to either FLEX (flexible) or CURR (current) duty hour standards. The FLEX regimen has three conditions for all internal medicine trainees: 80 hours maximum duty per week, 1 day off in 7, and in-house call no more frequent than every 3rd night (all averaged over a 4-week period). The primary outcome is 30-day mortality among Medicare beneficiaries. Additional outcomes include measures of patient safety and costs, trainee education, and intern sleep and alertness.

DSMB Charter

The charge to the DSMB and the board's charter were reviewed and discussed. The DSMB had questions about the DSMB's role in overseeing the study and the relationship of their charge for parent study and sub-study oversight. There were questions about the study timeline.

Background, origin, and overall design:
The parent and substudies were described and discussed, including the rationale for starting the parent study in July 2015 (prior to NHLBI funding) and the involvement of the ACGME. Relevant literature was reviewed and the CCC confirmed that future DSMB meetings would include an update on relevant literature.

Statistical Analysis Plan
An overview was reviewed. Points of discussion included the possibility of intern program selection bias because of the program's duty hour assignment, variability in the primary outcome across programs and implication for data analysis methodology, how the non-inferiority margin was selected, and rationale for the non-inferiority design. The potential value of a hierarchical model to account for clustering was discussed.

Mortality and Patient Safety Aim (Parent Study)
Points of discussion included the possibility for interim analyses for patient safety during the intervention period, differences between the planned unadjusted primary analysis and the severity-adjusted secondary analyses, the timeline for availability of mortality and patient safety data, and the timeline for data analysis.

Sleep and Alertness Aim (Substudy)

Points of discussion included the hypotheses and outcome measures, data acquisition and analysis plans, and actigraphy performance and reproducibility.

Education Aim

Points of discussion included the hypotheses and outcome measures, the use of observers in the time and motion sub-study, and the tacit consent language included in the surveys.

Data and Safety Monitoring Plan

Points of discussion included the fact that Medicare data to assess patient safety would not be available until after intervention completion, the mechanism for identifying adverse events in residents, the types of reportable events, and the format and process for reporting events to the DSMB.

Data Monitoring and Data Management

Points of discussion included the feasibility of interim monitoring for the primary outcome, monitoring safety and performance data throughout the trial, monitoring outcomes data that may be available during the trial year, integration of the multiple data sources, the responsibilities of both the CCC and DCC in data management, and reproducibility of the time and motion sub-study data.

Sub-study consent forms
Template informed consent forms were reviewed and discussed.

Closed Session: The DSMB did not hold closed session.

Executive Session (DSMB Members, NHLBI Executive Secretary, NHLBI Statistician):

The Board met in executive session to consider all information that had been presented and discussed, and to hold additional discussion and make recommendations.

RECOMMENDATIONS:

- The Parent study may continue without change to the protocol.
- The Sleep and Alertness sub-study portion of the protocol and informed consent are approved.
- The Time and Motion sub-study portion of the protocol and informed consent are approved.
- The DSMB concurs with the proposal for no planned interim analyses for the primary outcome for patient level data, given the timing of patient mortality data availability.
- The DSMB does not have any concerns regarding the role that the ACGME (which is co-funding the study) and FMCSA (which is loaning actigraphs and smartphones to the study) are playing in the study.
- The DSMB charter should more specifically describe the DSMB's role in overseeing the parent study and sub-studies as well as the study timeline.
- The Data and Safety Monitoring Plan (DSMP) should be modified so that a resident death is reported within 24 hours of iCOMPARE investigators' awareness of the event. The DSMP should clarify that the Chair, Dr. Logio, who agreed to serve as Medical Officer for the DSMB, and the NHLBI Executive Secretary will receive events that are reported in an expedited manner.
- The statistical analysis plan (SAP) should include more detail. How will the study adjust for site, geography, or patient mix characteristics that could impact mortality outcome? A hierarchical analysis should be considered.
- A data collection matrix table that clarifies the timeline for data collection of all variables for the parent and sub-studies should be submitted to the DSMB and added as an amendment to the protocol.
- The revised DSMB charter, DSMP, SAP, and data collection matrix should be submitted to the DSMB within one month. These revisions should not prevent the trial from continuing or the sub-studies from starting enrollment. An email ballot should be used to obtain final approval/disapproval of the items from the DSMB.
- The investigators should assess actigraphy performance and reproducibility during the study.
- The word "never" should be removed from the tacit consent language in the surveys.
- The investigators may consider obtaining a certificate of confidentiality for the surveys if feasible.

NEXT MEETING

The next meeting will be scheduled in 6 months as a teleconference/webinar. The DSMB will be review study progress, reports of data collection completeness and quality, enrollment data, safety data, and an update on any relevant literature.

SIGNATURES
These minutes accurately reflect the deliberation of the October 13, 2015 teleconference/webinar meeting.

See email approval — 10/16/2015

O. Dale Williams, Ph.D.
Chair, iCOMPARE DSMB — Date

10/16/2015

Carol Blaisdell, M.D.
Executive Secretary, iCOMPARE DSMB — Date

_xxxx__ Approve _____ Disapprove

10/16/2015

James P. Kiley, Ph.D.
Director, Division of Lung Diseases
NHLBI — Date