Summary of Oct. 3rd Presentations

Improving the System of Reporting and Interpreting Unexpected Serious Adverse Events to Investigators Conducting Research Under an IND
Goals of Project

- Generate empirical evidence about the current U.S. system for reporting unexpected serious adverse events to investigators conducting research under an investigational new drug application

- Consider potential modifications of the current system to more efficiently and effectively inform investigators of these events
Specific Objectives

1. Document the current range of practices for safety monitoring and reporting of unexpected SAEs to investigators (Workstream 1)

2. Quantify resources required to manage individual expedited safety reports and assess investigators’ perceptions regarding the value of this information (Workstream 2)

3. Compare current practice of submitting individual unexpected SAEs with an alternative approach based on the European Commission's guidance (Workstream 3)
Specific Objectives

4. Explore patients' expectations for how investigators should monitor and communicate information about product safety during the conduct of a clinical trial, and explore current practice on how safety monitoring efforts are being conveyed to research participants in the informed consent document (**Workstream 4**) 

5. Integrate results of all workstreams and recommend ways to optimize reporting of SAEs to investigators while ensuring human subjects protection (**Workstream 5**)
Organization of Project

Project Managers
- Cheri Janning
  Sr Clinical Project Manager
  Duke University
- Greg Nadzan
  Project Manager
  Amgen, Inc.

Reporting Unexpected, Serious Adverse Events to Investigators
- Jose Vega
  Amgen Co Team Leader
- Kathleen Uhl
  FDA Co Team Leader
- Susan Ellenberg
  Univ. of Pennsylvania Co Team Leader

Workstream 1
- Sundeep Sethi
  Amgen Workstream 1 Lead
- Lynda Szczech
  Duke Clinical Research Institute Workstream 3 Lead
- Robert Califf
  Duke Translational Medicine Institute Workstream 5 Lead
- Workstream 1 Team
- Workstream 3 Team
- Workstream 5 Team

Workstream 2
- Howard Greenberg
  ACCP/Clinilabs Workstream 2 Lead
- Kevin Weinfurt
  Duke Clinical Research Institute Workstream 4 Lead
- Workstream 2 Team
- Workstream 4 Team
Workstream 1

Document current range of practices for safety monitoring and reporting unexpected SAEs to investigators

- Industry sponsors emphasize safety notifications to investigators using individual expedited reports
- Industry sponsors have well-developed mechanisms for IND safety data management including drug safety units/clinicians, written standard procedures, and use of external bodies to manage and review the data
- Investigators voiced concerns to sponsors including dissatisfaction with volume (too many) and content (not relevant) of individual IND safety reports
- Recommend encouraging aggregate safety notifications from sponsors to investigators and reducing investigator burden of unnecessary individual expedited reports
Workstream 2

Quantify resources and assess value of individual expedited safety reports

- Resource estimate of $22/SAE evaluated with CI of $10-$33 (0.25hr median with CI of 0.12-0.38 hrs/SAE). Sensitivity analysis gives range of $7-49/SAE.
- Low perceived value of individual SAE reports due to lack of context (incidence, relatedness) for events
- “Contextual” information is useful:
  - Data Monitoring Committee (DMC) reports
  - Notification letter of unanticipated problem (~UADE or suspected adverse reaction in FDA guidances of 1/09 and 9/10)
- Increased use of DMCs and FDA Guidance may assist investigators, sponsors, and IRBs focus on events likely to impact patient safety
Workstream 3

Compare current practice of submitting individual expedited reports with alternative approach used in European Union

- Small number of respondents and small number of reportable events in this workstream limit conclusions
- Data suggest a potential time savings afforded to investigators by aggregate reporting of individual events
Workstream 4

Explore patients’ expectations for safety monitoring and communication as well as how safety monitoring efforts are being conveyed to participants in the informed consent document.

Recommendations:

- Increase patients’ understanding about clinical trials and how risks are managed
- Language in consent forms should reflect reality
- Need to address conflicts of interest to restore/maintain trust
Objectives of October 3\textsuperscript{rd}/4\textsuperscript{th} meeting (see Agenda)

- Discuss and integrate empirical findings from all components of this project
- Consider implications of the US FDA’s new premarket safety regulations
- Develop a set of recommendations for optimal reporting of unexpected serious adverse events to investigators that will improve human subjects’ protection
Questions to Consider

- Can you envision an alternative model for reporting important new safety information to investigators and patients during the conduct of a clinical trial?

- How can we better evaluate safety of an investigational product across multiple clinical trials and indications for use?