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

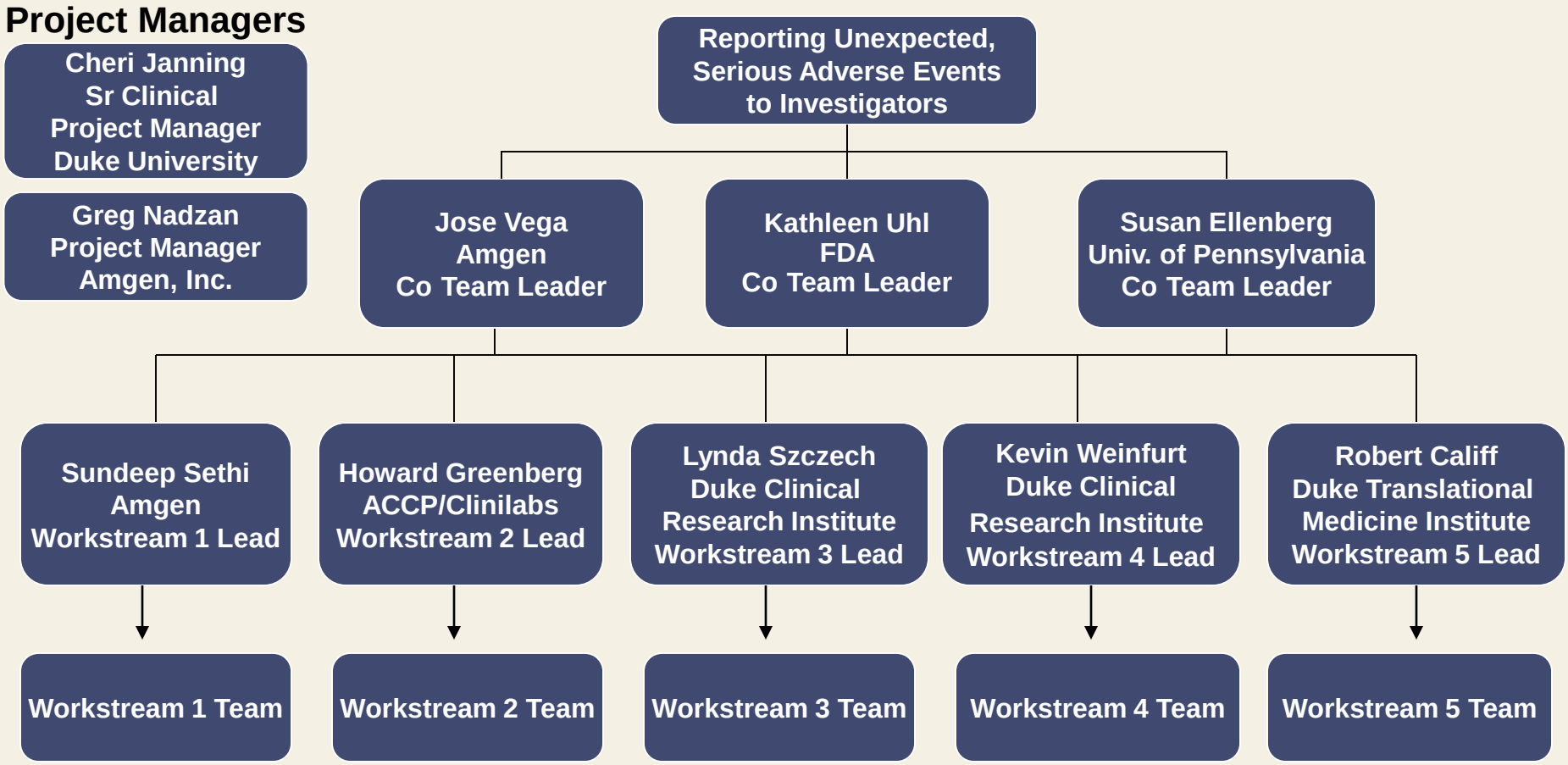
1. **Document the current range of practices for safety monitoring and reporting of unexpected SAEs to investigators (Workstream 1)**
2. **Quantify resources required to manage individual expedited safety reports and assess investigators' perceptions regarding the value of this information (Workstream 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



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 3rd/4th 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?