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

A project of the Clinical Trials Transformation Initiative

Background

- Investigators conducting research under an IND have voiced concerns over current approaches to notifying them of unexpected and serious adverse events (SAE)
- Current regulations* (21 CFR 312.32) require IND sponsors to notify investigators of all unexpected SAEs associated with the drug
- Common practice is to provide all unexpected (per investigators' brochure) SAEs as individual expedited reports
  - Contextualizing unexpected SAE difficult across indications and regimens

* Prior to new premarket safety regulations effective March 2011

Background (continued)

- **Result: significant investigator investment of time for little-to-no gain in understanding risk-benefit of investigational product**
  - **Process can distract investigators from direct care of study participants and more meaningful communication of safety data**
- **FDA Guidance addresses similar issue for IRBs, but no corresponding guidance exists for investigators' safety notifications**

Goals

- **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

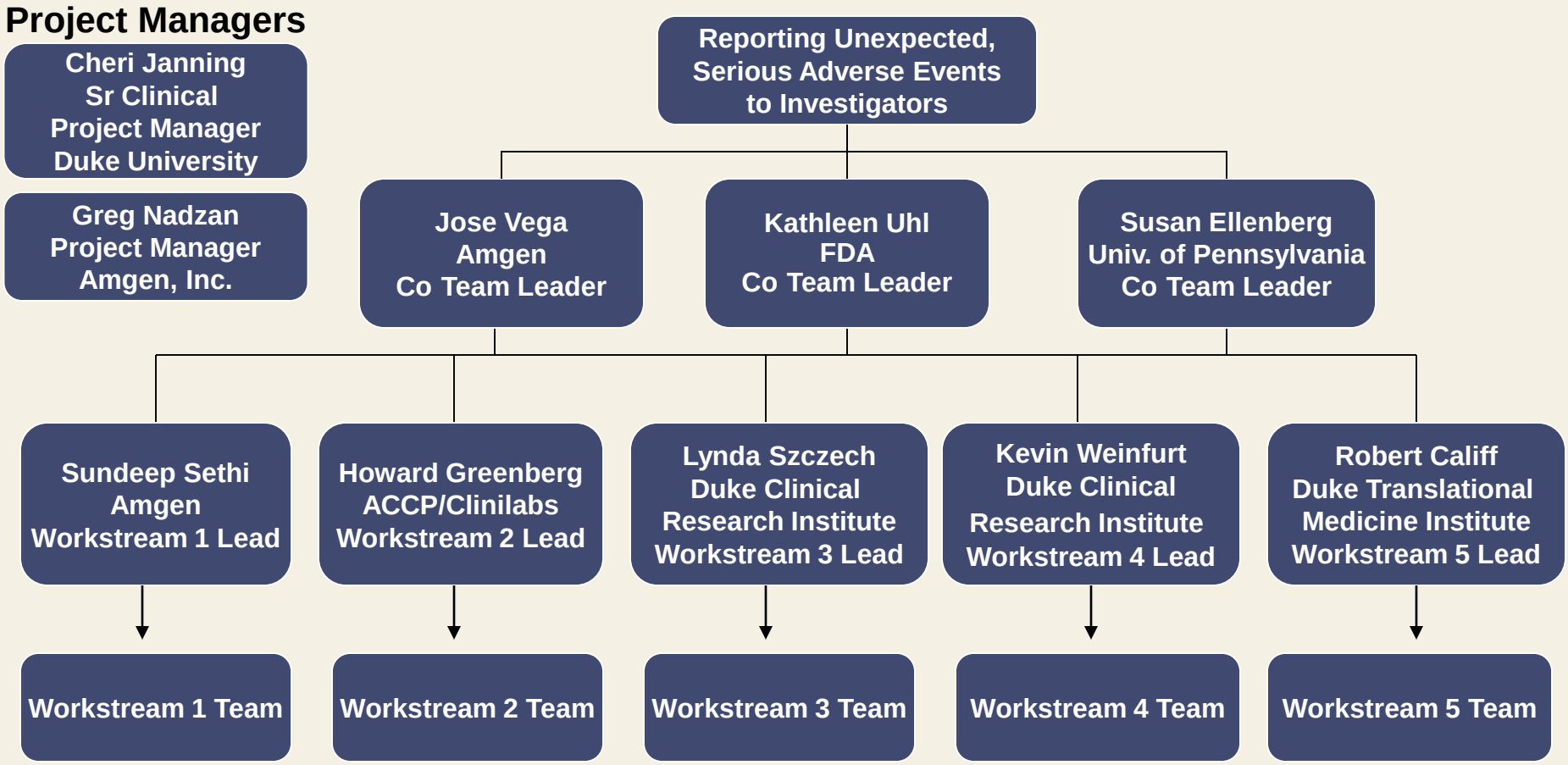
1. **Document the current range of practices for safety monitoring and reporting of unexpected SAEs to investigators (Workstream 1)**
2. **Quantify resources required to manage individual expedited safety reports and assess investigators' perceptions regarding the value of this information (Workstream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

- Philippe Bishop (Roche)
- Dorothy DiChristofano (Sanofi-Aventis)
- Leann Fieldstad (Roche)
- Suzanne Gagnon (ICON Clinical Research)
- Greg Hockel (PharmaNet)
- Anne Meeker-O'Connell (FDA)
- Greg Nadzan (Amgen)
- Diane Ryan (Pfizer)
- Sundeep Sethi – Workstream Lead (Amgen)
- Jennifer Sorgen (Pfizer)
- Jose Vega (Amgen)

Workstream 2 Team

- Susan Ellenberg (UPenn)
- Howard Greenberg – Workstream Lead (ACCP / Clinilabs)
- Greg Hockel (PharmaNet)
- Kevin Jones (Accurate Clinical Trials)
- Greg Nadzan (Amgen)
- Janet Norden (FDA)
- Diane Ryan (Pfizer)
- Miklos Salgo (Roche)
- Sundeep Sethi (Amgen)
- Lynda Szczech (Duke)
- David Vock (Duke)

Workstream 3 Team

- Suzanne Gagnon (ICON Clinical Research)
- Heather Macy (Pfizer)
- Rachpal Malhotra (Bristol-Myers Squibb)
- Margaret McLaughlin (Pfizer)
- Greg Nadzan (Amgen)
- Leonard Sacks (FDA)
- Sundeep Sethi (Amgen)
- Lynda Szczech – Workstream Lead (Duke)
- Jose Vega (Amgen)

Workstream 4 Team

- **Kathryn Flynn (Duke)**
- **Kevin Weinfurt – Workstream Lead (Duke)**

Workstream 5 Team

- **Robert Califf (Workstream Lead)**
- **Susan Ellenberg**
- **Howard Greenberg**
- **Judith Kramer**
- **Janet Norden**
- **Sundeep Sethi**
- **Kathleen Uhl**
- **Jose Vega**

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**