



# Timely Reporting of Problems in NIH Intramural Clinical Research Protocols

January 13, 2017

**Michael Gottesman, M.D.**

**Andrew Griffith, M.D., Ph.D.**

**Lawrence A. Tabak, D.D.S, Ph.D.**



**Intramural Research Program**

*Our Research Changes Lives*

**one program  
many people  
infinite possibilities**



# Recent Late Reporting Event

- NCI clinical trial of ibrutinib for central nervous system lymphoma
- Overall, trial showed high remission rate
- But, high incidence of aspergillosis resulting in deaths
- Late reporting of UPs and SAEs/UPs to IRB and sponsor
- FDA issuance of 483

# Serious Adverse Event (SAE)

- **Adverse Event (AE):** Any untoward or unfavorable medical occurrence in a human subject...whether or not considered related to the subject's participation in the research
- **SAE:**
  - Results in death
  - Is life-threatening
  - Results in inpatient hospitalization or prolongation of existing hospitalization
  - Results in a persistent or significant disability/incapacity
  - Results in a congenital anomaly/birth defect

**OR**

- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

# Unanticipated Problem (UP)

**Any incident, experience, or outcome that meets all of the following criteria:**

- Unexpected
- Related or possibly related to participation in the research
- Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized
- Vast range of UPs reported by NIH IRBs
  - Use of outdated consent with no interval changes
  - Death possibly related to study drug

# Trans-NIH Survey: Timeliness of SAE and UP Reporting

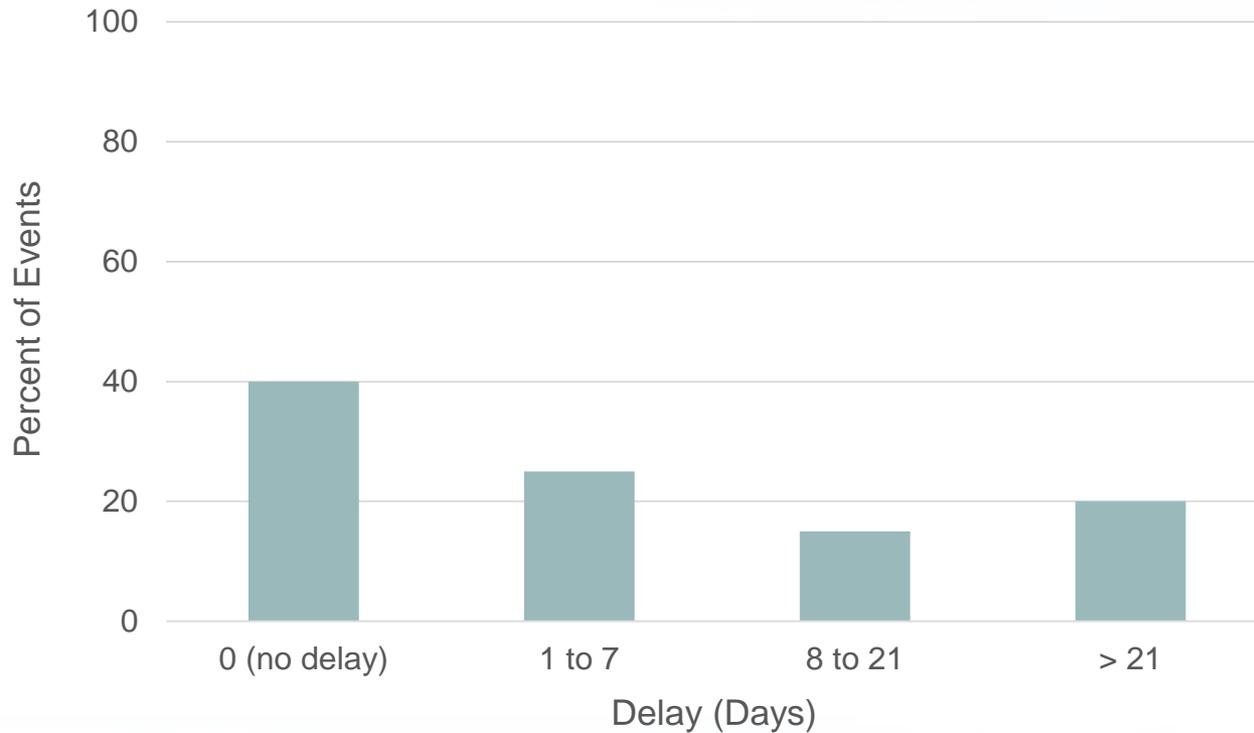
- Based on the findings of late reporting in the NCI Clinical Trial, the NIH Office of Research Support and Compliance (ORSC) coordinated a trans-NIH survey
  - Timeliness of reporting of SAEs, UPs, or SAE/UPs to IRB or study sponsor
  - Included all interventional and/or FDA-regulated studies open to enrollment or follow-up from 10/1/13 – 10/1/16
  - Data **self-reported and still preliminary**
    - PIs and Institutes/Centers (ICs) responsible for determining how to identify applicable events and applicable reporting deadlines

# Trans-NIH Survey: Overall Results (Preliminary)

- Late reporting to IRB, sponsor, or both
  - Eligible protocols: 711 (out of ~1575 total protocols)
  - Events: 3,615
  - Protocols with at least one event reported late: 274 (39%)
  - ICs with late reporting: 15
- ***Late reporting is not an isolated event within the NIH intramural clinical research program***

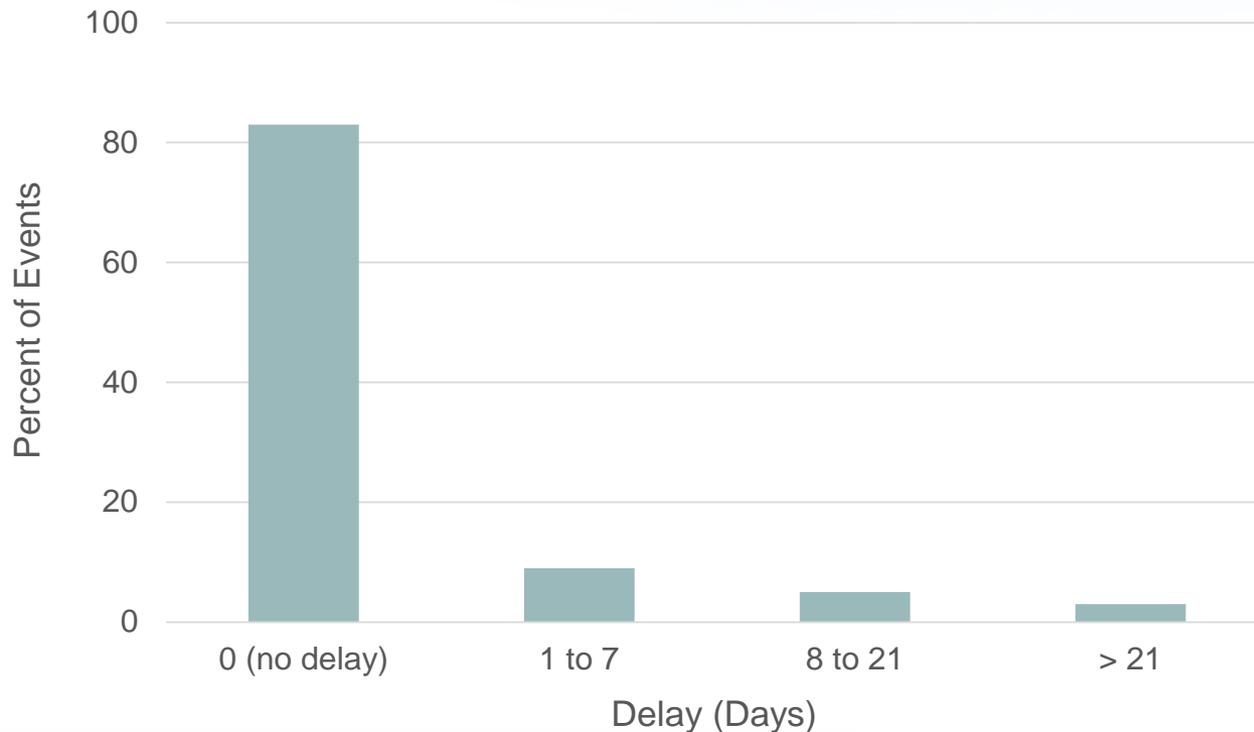
# Trans-NIH Survey: IRB Reporting (Preliminary)

Majority of UPs and UP/SAEs were reported late to the IRB



# Trans-NIH Survey: Sponsor Reporting (Preliminary)

17% of SAEs and UP/SAEs were reported late to the sponsor



# Immediate Action Plan: Protocol Audit

## Trans-NIH independent audit:

- Sample frame: 10% of all interventional protocols
- Performed by independent contract research organization
- **Timeline:**
  - Anticipated to begin in the first quarter of 2017
  - Complete by mid- to late 2017

# Short-Term Action Plan: Procedures

- Conduct daily (or weekly) rounds for prompt recognition of reportable events
  - Possibly combine with safety rounds
  - **Timeline:** Late January 2017
- Institute standard operating procedures (SOPs) for every IC to monitor and assure proper and timely reporting
  - **Timeline:** February 2017; periodic reviews/audits thereafter
- Initiate cross-checking for event reporting to IRB, study sponsor, and/or FDA
  - **Timeline:** March 2017

# Short-Term Action Plan: Staff Education

*PI is responsible for reporting, but all staff must understand the critical nature of their role in reporting events*

- Thorough education of research team
  - Develop education campaign (posters, etc.) for team approach to detection and reporting
    - **Timeline:** Launch in March/April 2017
  - Implement team training and periodic refreshers for ALL studies to ensure entire team is aware of protocol procedures and reporting requirements
    - **Timeline:** Launch in April 2017; ongoing thereafter

# Short-Term Action Plan: Reinforcement of Responsibility

- Empower IRBs to detect and respond to late reporting
  - **Timeline:** January 2017
- Modify PMAP (performance plan) elements for IC Directors, Clinical Directors, principal investigators, research nurses and other team members
  - Include minimal benchmark for tracking and timely reporting of events
  - **Timeline:** Incorporate into mid-year review – June/July 2017
- Establish consequences to PIs of poor compliance:
  - Appearance before Medical Executive Committee
  - Meetings with escalating levels of IC leadership:
    1. Clinical Director
    2. IC Director
    3. DDIR and DDICR
    4. NIH Director and/or Principal Deputy Director
  - **Timeline:**
    - Develop implementation plan by March 2017
    - Implement in mid-2017

# Mid-Term Action Plan: Infrastructure

## Personnel:

- Ensure that every PI has access to a Protocol Navigator
  - IC-based versus central (e.g., Clinical Center)?

## Information Technology:

- Institute a compliant electronic database for every protocol
- Launch a single protocol tracking system across NIH

## Timeline (Personnel and IT):

- Develop implementation plans by the end of February 2017
- Implement plans by the end of 2017

# Longer-Term Action Plan

## Assure Uniformity and Central Oversight of Clinical Research

- Current structure:
  - 17 ICs with intramural programs that conduct clinical research
  - 12 IRB panels that review this research
- Office of Intramural Research has responsibility for:
  - Central oversight of human subjects protections (OHSRP)
  - All clinical studies and facilities that support these studies (ORSC)
- Centralization should occur in two domains:
  - Centralize clinical research support (protocol navigators, quality control, monitoring, etc.)
  - Reorganize IRBs with central governance and management; merge OHSRP and ORSC