Timely Reporting of Problems in NIH Intramural Clinical Research Protocols

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Michael Gottesman, M.D.
Andrew Griffith, M.D., Ph.D.
Lawrence A. Tabak, D.D.S, Ph.D.
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
  - 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  - Use of outdated consent with no interval changes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
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
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