Facilitating Human Subject's Research: NCI CIRB Initiative Open Forum

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Improving Efficiency in NCI/DCTD-Sponsored Clinical Trials: Timelines, Central IRB and Unified Data Collection

Joint BSA/NCAB Meeting
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Three Initiatives to Improve Efficiency in NCI/CTEP-Sponsored Clinical Trials

- OEWG Timelines: Rapid initiation of clinical trials
- NCI Central Institutional Review Board (CIRB)
- Electronic data capture and management system
In March 2010, the OEWG provided recommendations to the NCI on strategies to decrease the time required to activate NCI-sponsored clinical trials.

A major component of the recommendations was the creation of target timelines and absolute deadlines for studies to go from Concept/LOI submission to activation (activation defined as study open to patient enrollment).

- **Phase 1 and 2 Studies:**
  - Target Timeline – 210 days
  - Absolute Deadline – 540 days \(\text{Now 450 days}\)

- **Phase 3 Studies:**
  - Target Timeline – 300 days
  - Absolute Deadline – 730 days \(\text{Now 540 days}\)
NCI/DCTD/CTEP Response

• Project Managers were hired to closely track study timelines.

• Secure website developed to allow investigators, operations staff, and NCI staff to monitor timelines.

• Routine conference calls between NCI reviewers and external investigators instituted at key points in the review process to quickly resolve issues and decrease the need for multiple document revisions.

• Medical Editors were hired with responsibilities including compiling and editing Consensus Reviews and inserting applicable revisions directly into an unofficial copy of the Protocol using Track Changes®, thus saving investigators valuable time.

• At Cancer Centers and Cooperative Groups, similar staff, process and IT changes were instituted.
Calls between study team & NCI to clarify/discuss Consensus Review to prevent review iterations that may slow the approval process

Conference calls occur at several key points:
- LOI’s: on-hold, approved pending drug company review, or approved
- Concepts: pending response to Steering Cmte evaluation or approved
- Protocols: pending response to Consensus Review
- Ad Hoc: as special issues arise during study development process

Approximately **480** conference calls between April 2010 – May 2012:
- 189 calls for LOI’s
- 99 calls for Concepts
- 174 calls for Protocols
Timeline Comparison of Study Activation for Early Phase Trials: Historical vs. Post-OEWG (Apr 2010 – May 2012)

Historical Studies (n=149 early phase studies activated between 2006 and 2008)
- Median: 524 days
- 95%: 5%

Post OEWG Studies (n= 66 early phase studies submitted after April 1, 2010)
- Median: 362 days
- 95%: 5%

OEWG Target
- Protocol Development Target: 90 days
- LOI Approval Target: 60 days
- Trial Activation Target: 90 days

Absolute Deadline: 540 Days
Breakdown of the study development stages

*Early Phase Studies*

- **LOI submission to LOI approval** (n=108)
  - Historical Data: 101 days
  - Post-OEWG Data: 62 days
  - Target: 60 days
  - 95% completion in 101 days
  - 5% completion in 62 days

- **LOI approval to Protocol submission** (n=102)
  - Historical Data: 63 days
  - Post-OEWG Data: 60 days
  - Target: 60 days
  - 95% completion in 60 days
  - 5% completion in 63 days

- **Protocol submission to Trial activation** (n=66)
  - Historical Data: 285 days
  - Post-OEWG Data: 220 days
  - Target: 90 days
  - 95% completion in 285 days
  - 5% completion in 220 days
Timeline Comparison of Study Activation for Phase III Trials: Historical vs. Post-OEWG (Apr 2010 – May 2012)

Historical Studies (n=67 phase 3 studies activated between 2006 and 2008)
- Median: 829 days

Post OEWG Studies (n= 8 phase 3 studies submitted after April 1, 2010)
- Target Timeline: 300 Days
  - Concept Approval Target: 90 days
  - Protocol Development Target: 90 days
  - Trial Activation Target: 120 days
  - 95% within 320 days

Absolute Deadline: 730 Days

OEWG Target
- 95% within 960 days
Background – NCI Chooses an IRB Model

- OHRP IRB model choices
  - *Independent/Stand-Alone IRB model*
    - Appropriate where no local IRB exists
    - Understanding of local context obtained via worksheets, site visits, audits, teleconferences
  - *Shared responsibilities model*
    - More appropriate where local IRB already present
    - Can utilize LIRB for understanding of local context
    - No need for site visits, etc.

- In consultation with OHRP, NCI designed a shared responsibilities model that is compliant with Federal Regulations regarding Cooperative Research (45 CFR 46.114)
  - *CIRB’s primary function is initial and continuing review of studies, including amendments*
  - *The local institution’s primary function is consideration of local context, oversight of local performance*
How it Works: CIRB Review to Study Activation

- CIRB receives new study, ICD, completed CIRB Application and any other review material from the Cooperative Group Study Chair (national PI).

- CIRB conducts review
  - Any back and forth/request for changes is between Study Chair and CIRB until CIRB approves trial.

- Cooperative Group activates study and CIRB posts documents

- Enrolled IRB may then conduct Facilitated Review instead of full board local IRB review.
  - “Facilitated Review” – the review during which the local IRB reviews the CIRB-approved study for local context considerations
CIRB Profile - Enrollment

- Enrollment is open to IRBs reviewing Cooperative Group Studies

- Number of Signatory Institutions Enrolled 330
  - Number of Institutions using Adult CIRB only 183
  - Number of Institutions using Pediatric CIRB only 42
  - Number of Institutions using both Adult & Pediatric CIRB 105

- Total Number of Enrolled Signatory Institutions, Affiliates, and Components 1,023

- Number of NCI Designated Cancer Centers 43
- Number of CCOPs 35
- Number of MBCCOPs 10

Current as of 04/30/2012
CIRB Profile - Utilization

- **Number of Facilitated Reviews Reported**: 14,987
  - One Facilitated Review indicates one IRB has used the CIRB’s review to open one study thus saving one full board review.
    - 14,987 FRs reported indicates enrolled IRBs have used the CIRB’s reviews and saved the time and effort associated with conducting 14,987 full board reviews.

- **Number of Studies Available for Facilitated Review**: 292
  - **Adult**: 183
  - **Pediatric**: 109
Costs and Benefits of the NCI CIRB (Todd Wagner, PhD, economist, VA Palo Alto and Stanford University, Journal of Clinical Oncology Feb. 2010)

- Surveyed local researchers and IRB staff at affiliated and non-affiliated sites to understand effort, time and cost
- For initial reviews, CIRB affiliation was associated with
  - 6.1 hours research staff effort saved
  - 2.3 hours less effort for IRB staff
  - 34 days faster from the date the research staff started the paperwork until IRB approval
  - $717 saved per review
Top Ten Institutions (by Facilitated Reviews Reported for Adult Studies)

- West Michigan Cancer Center 132
- University Medical Center of Southern Nevada 117
- Gundersen Clinic, Ltd 115
- Saint Joseph Mercy Health System 108
- Aultman Health Foundation 105
- Georgetown University 101
- St. Vincent Hospital 100
- Advocate Health Care Network 98
- Mission Health Systems 96
- Thomas Jefferson University 93

Current as of 04/30/2012
Top Ten Institutions (by Facilitated Reviews Reported for Pediatric Studies)

- University of California San Francisco 97
- All Children’s Health System, Inc. 93
- The Children’s Hospital of Philadelphia 89
- Hackensack University Medical Center 87
- Children’s Hospital Central California 84
- Children’s Hospital of Wisconsin 84
- Washington University St. In St. Louis 83
- Children’s National Medical Center 82
- Children’s Memorial Hospital 81
- University of New Mexico Health Sciences Center 80
- Nationwide Children’s Hospital 80

Current as of 04/30/2012
Typical CIRB Composition

- One Chair and 14 Voting Members (15 Total)

  Patient Advocates  4 (25%)
  Physicians         8 (50%)
  Other Professionals 4 (25%)

  Nurses            1
  Pharmacist       1
  Statistician     1
  Ethicist         1
Key Features of Possible Model Change

- **NCI** is considering a change to an “Independent Model”
  - *CIRB reviews local context for IRBs* (No more ‘facilitated review’)
    - CIRB informed of local context considerations via Worksheets completed by each institution and every investigator who opens a study
    - *CIRB would be IRB of Record for a study at an institution*

- **Rationale**
  - *Should increase CIRB enrollment and utilization*
    - NCI wants to improve clinical trial efficiency
    - Greater societal benefit
      - Faster IRB approval for investigators
      - Faster accrual and trial completion
    - *Positions the CIRB well for AAHRPP accreditation*

- **Pilot Study**
  - *Inform NCI re impact on local institutions, feasibility, best practices*
  - *Population – about 25 institutions (enrolled using Adult CIRB, Pediatric CIRB, or both CIRBs; currently not enrolled)*
  - *Study Duration*
    - July 2011 through September 2012
Key Features of Possible Model Change

- **Profile of Pilot Study**
  - **24 Institutions participating**
    - 14 previously using the “facilitated review” model
      - 9 using Adult CIRB only
      - 9 using PedCIRB only
      - 6 using both Adult and PedCIRB
    - 2 not previously enrolled and using the CIRB for the first time

- **Number of Studies Opened in Pilot as of 6/6**
  - 1,218 “facilitated reviews” transferred into new model
  - 127 studies opened in new model

- **Feedback from helpdesk**
  - **Enthusiasm of participants high**

- **Contractor assumed additional tasks to recruit pilot sites, transfer their studies into new model, provide support to sites and track pilot metrics**
Evaluation Activities

• **Evaluation by NCI’s Office of Market Research and Evaluation**
  – *Surveys gathered from institutional representatives at three timepoints – prior to study, mid-study, end of study*
  – *Respondents include IRB Chairs, Investigators, IRB staff*
  – *Results report due end of third quarter 2012*

• **Sampling of Metrics tracked by CIRB Operations Office**
  – *Study-specific data*
    • Number of ‘facilitated reviews’ transferred into new model (1,218)
    • Number of new studies opened using independent model as of 6/6 (127)
  – *‘Length of review’ milestones*
    • Both internal Operations Office pre-review as well as CIRB reviews
  – *Frequency of special reviews*
    • “Unanticipated problems”
    • Locally-developed recruitment materials

• **Final decision on CIRB model to be used going forward - Late 2012**
Expansion of CIRB Menu

- CIRB to review studies opened in new Early Trials Clinical Trials Network
- Institutions to participate via contract mechanism
  - *U01 contracts for early clinical trials: Phase 0, 1, and early 2*
  - *N01 contracts for Phase 2 trials*
- CIRB requested to review to ensure trials opened within 4 weeks
- Involves about 50 new studies/year
- Necessitates another CIRB dedicated to review of these early trials
  - *Will require recruitment of qualified members and operations staff*
- RFA to be released end of 2012/early 2013; awarded early 2014; trial review begins mid-2014
Advantages of using the NCI CIRB (regardless of model or menu)

- **Benefits patients and research participants**
  - Oncology-specific, multidisciplinary Boards
  - Dedicated review for study participant protections
  - Opens trials faster
  - Easier to open trials for rare diseases

- **Benefits for Investigators and research staff**
  - Eliminates back-and-forth with IRB to gain study approval
  - Eliminates frequent subsequent submissions for amendments, continuing reviews, adverse events, etc.
  - Eliminates or reduces
    - Completing IRB application
    - Compiling and duplicating IRB submissions

- **Benefits for IRB members**
  - Saves IRB members’ time and effort
    - Eliminates full board review of Cooperative Group trials

- **CIRB Website URL:** [www.ncicirb.org](http://www.ncicirb.org)
What is a Clinical Data Management System (CDMS)?

- **Tool(s) or processes that support:**
  - Data collection
    - Remote Data Capture (RDC)
  - Data coding
    - Standard libraries - Common Toxicity Criteria (CTCAE)
  - Data management
    - Discrepancy, delinquency, communication, correction
  - Preparation of data for analysis
A CDMS directly/indirectly effects the entire research organization

Areas effected:
- Science
- Safety
- Regulatory
- Administration
- Operations
- Financial management

Individuals effected:
- Group Chair
- Statistical office
- Operations office
- Study principal investigator (PI)
- Participating sites/research staff
  - Physicians, nurses, CRAs
- Patient
Effect of multiple CDMS’s on NCI mult-center trial system

- Increased training costs
- Increased risk of data delinquency and/or discrepancy
- Increased time/effort to correct/complete data
- Delays in obtaining Science and Safety results
The Need

- IOM report states: More resources for the rapid implementation and adoption of a common electronic registration and data capture system would increase consistency across trials, conserve resources by:
  - Reducing the workload associated with patient enrollment and follow-up
  - Allow for more timely review of the data from a trial
  - Enhance the knowledge gained from a trial
  - Standardized case report forms would ease the burden of regulatory oversight and lead to better compliance*

*A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program: Sharyl J. Nass, Harold L. Moses, and John Mendelsohn, Editors; Committee on Cancer Clinical Trials and the NCI Cooperative Group Program; Institute of Medicine; Copyright © 2010*
Opportunity

• A strong foundation for CDMS uniformity across the Groups
  – Investigators/sites are often members of multiple Groups
  – All Group site/investigators can enroll patients on selected clinical trials through the CTSU

• Added emphasis
  – Federal funding constraints make it essential for sites to perform clinical trial functions with optimal efficiency
  – Transformation/consolidation of Groups
    • Further promotion of network collaboration
    • Merged Groups must select a common CDMS
The Vision for a Common CDMS

*Re-enforce focus on Science and the Patient NOT data management*

- Promote efficient and accurate data entry using a common intuitive/user-friendly interface
- Scalable for use for all Group Trials
  - Treatment (drug, surgery, radiation); Prevention; Cancer Control; Diagnostic
- Minimize training and implementation cost across Groups through shared training and experience
- Reduce data management burden/costs for multi-center coordinating center as well as participating sites
## Rave Subject Page

### Task Summary: Site
- **NonConformant Data**: 7 Subjects
- **Open Queries**: 73 Subjects
- **Overdue Data**: 0 Subjects

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Requirements to deploy a common CDMS to the Groups

Standard approach to:

• **Application** (Medidata Rave):
• **Core Configuration**:
• **Business practices**:
  • Data delinquency rules
• **Integration with ‘Global’ applications**:
  – Pt enrollment, NCI accrual and adverse event reporting, **User-name/password/Role (single sign-on)**
• **Case Report Forms**:
  – Cancer Data Standards Registry and Repository (caDSR)
Key Concepts for Successful Deployment

- Leverage experience
  - Medidata
  - Groups
    - General CDMS knowledge
    - Rave Specific: Alliance (2yr) and NCIC (5+yr)
- Strive for common look/feel of outward/community facing features
  - Single sign-on
  - Remote data capture (RDC)
- Standard interfaces require a standard approach
Organizations Adopting Common CDMS

- **Who:**
  - All NCI Cooperative Groups
  - COG Phase 1 Consortium
  - Adult Brain Tumor Consortium (ABTC)
  - Theradex (early phase 1)
  - Cancer Trials Support Unit (CTSU)

- **Role:**
  - Modify business, operational and technical infrastructure to implement Rave
  - Participate in standards development/adoption activities
  - Integrate local applications with Rave
  - “Local” knowledge acquisition
NCI

• Who
  – CTEP, DCP, CCCT, RRP, CIP, BRB, CBIIT

• Role
  – Project oversight
  – Establish overall direction and expectations
  – Promote standardization NOT standards
  – Resource allocation:
    • License
    • Hosting
    • Training
    • Maintenance
    • Contractor support
Deployment Plan (start 4/1/11)

Stage 1 0 to 90 days
- Start Apr 1, 2011
- First 3 sites (Alpha) begin deployment (start of stage)
  - Allow 1yr to implement

Stage 2 91 to 180 days
- Start Jul 1, 2011
- Second 3 sites (Bravo) begin deployment (start of stage)
  - 9-months to implement
  - Alpha sites continue deployment activities

Stage 3 181 to 270 days
- Start Oct 1, 2011
- Third 3 sites (Charlie) begin deployment (start of stage)
  - 9-months to implement
  - Bravo sites continue deployment activities
  - Alpha sites complete deployment (end of stage)

Implementation Alpha/Bravo 4/1/12
Charlie 7/1/12
Toxicity (Adverse Event) Page

Record all Grade 3 or higher AEs. Record only Unexpected Grade 2 AEs. Record Grades 1 and higher for all events listed in protocol section 8.1.1. Record each event only one time per cycle of treatment, identifying the highest grade of the event.

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Severe Adverse Event (SAE) Reporting for Cooperative Groups

**Problem:** Currently there is a dis-connect between ‘Routine’ Adverse Event (RAE) and Severe Adverse Event (SAE) reporting
- RAE and SAE data captured in separate systems
- Double data entry
- Promotes under/over reporting
- Discrepancy Reconciliation

**Solution:** Single source for reporting both RAE and SAE reporting (i.e. Rave)
- Enter AE one time (reduce/eliminate discrepancies)
- ‘Smart’ CRFs identify AEs that require additional information (SAEs)
- Reduce training requirements for site MD, RN, CRAs
Conclusion - Modernized/Standardized
Group CDMS will:

- Support/complement transformation of Groups into a ‘Network’
- Meets FDA and other Federal requirements for electronic data capture, security and transfer
- Reduce effort/cost of data management
- Improve trial management/decision-making
- Promote data sharing
- Sets the stage for potential further infrastructure improvements
  - SAE reporting; Remote auditing; electronic filing for FDA reports
Three Initiatives to Improve Efficiency in NCI/CTEP-Sponsored Clinical Trials

- OEWG Timelines: Rapid initiation of clinical trials
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- Electronic data capture and management system