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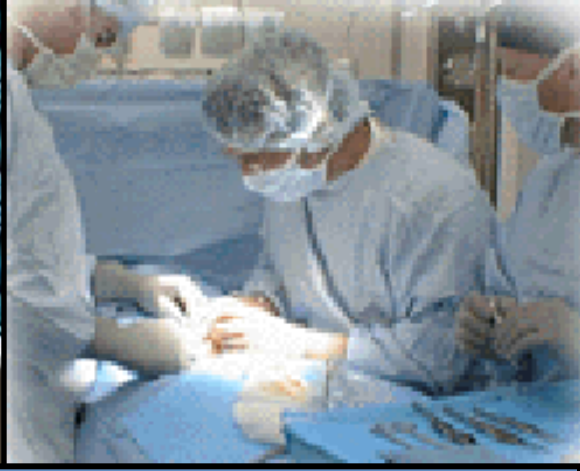

Improving Efficiency in NCI/DCTD-Sponsored Clinical Trials: Timelines, Central IRB and Unified Data Collection

Joint BSA/NCAB Meeting

June 25, 2012

Jeffrey Abrams, MD

Acting Director for Clinical Research

Division of Cancer Treatment and Diagnosis

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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**

OEWG - Background

- 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~~ **Now 450 days**

  - ➢ Phase 3 Studies:
    - Target Timeline – 300 days
    - Absolute Deadline – ~~730 days~~ **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

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OEWG Conference Call Process

- 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

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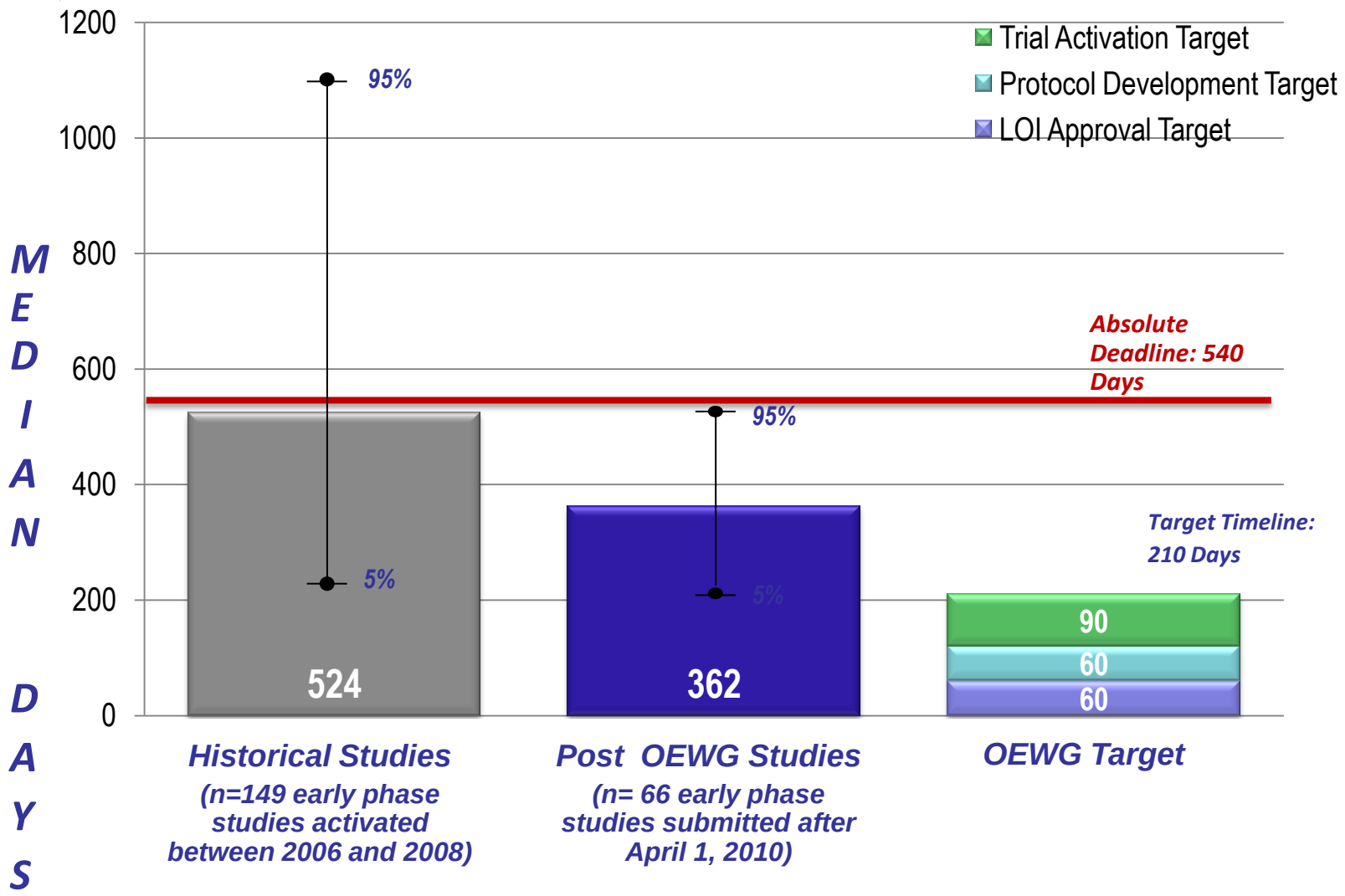
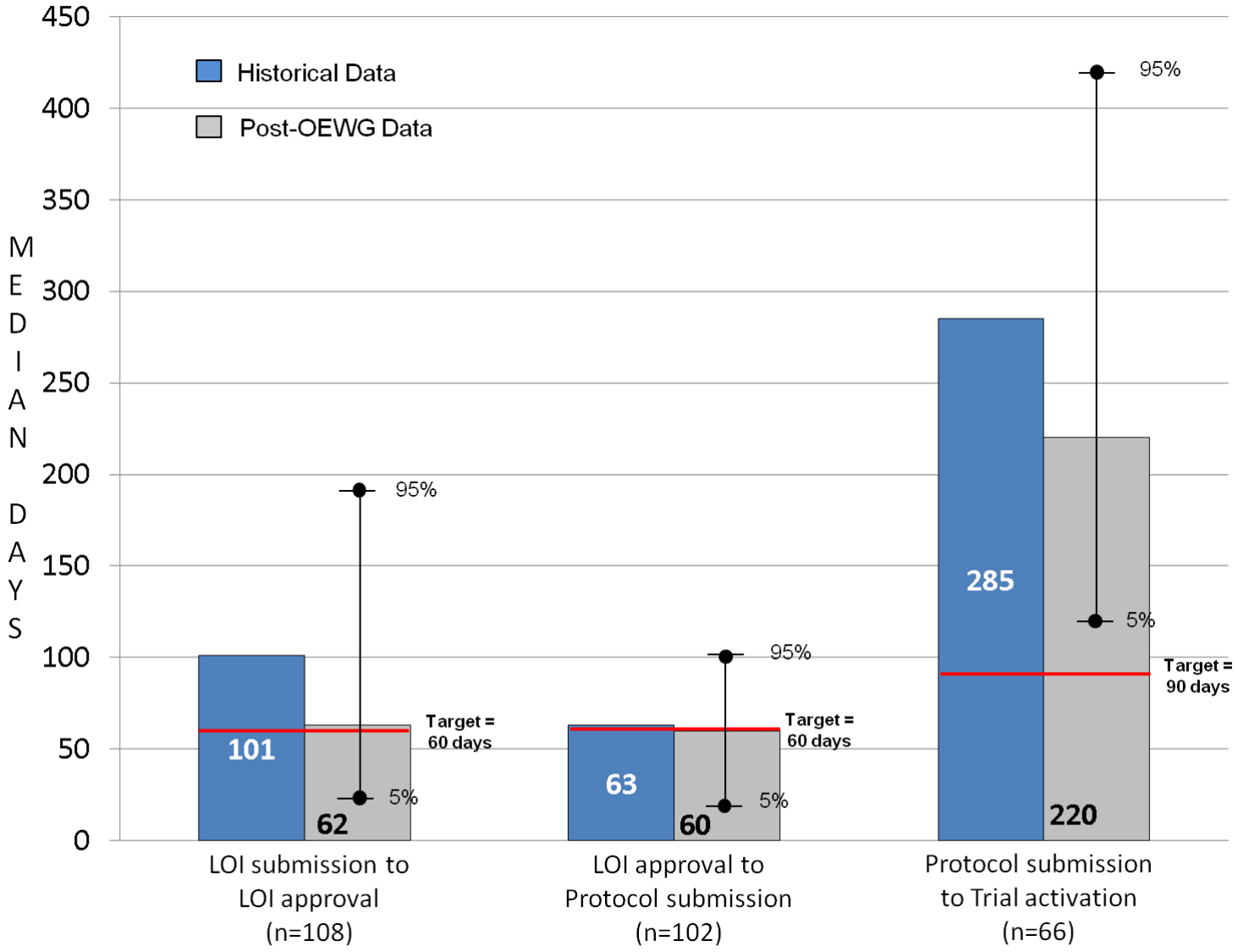
Timeline Comparison of Study Activation for Early Phase Trials: Historical vs. Post-OEWG (Apr 2010 – May 2012)



Breakdown of the study development stages
Early Phase Studies



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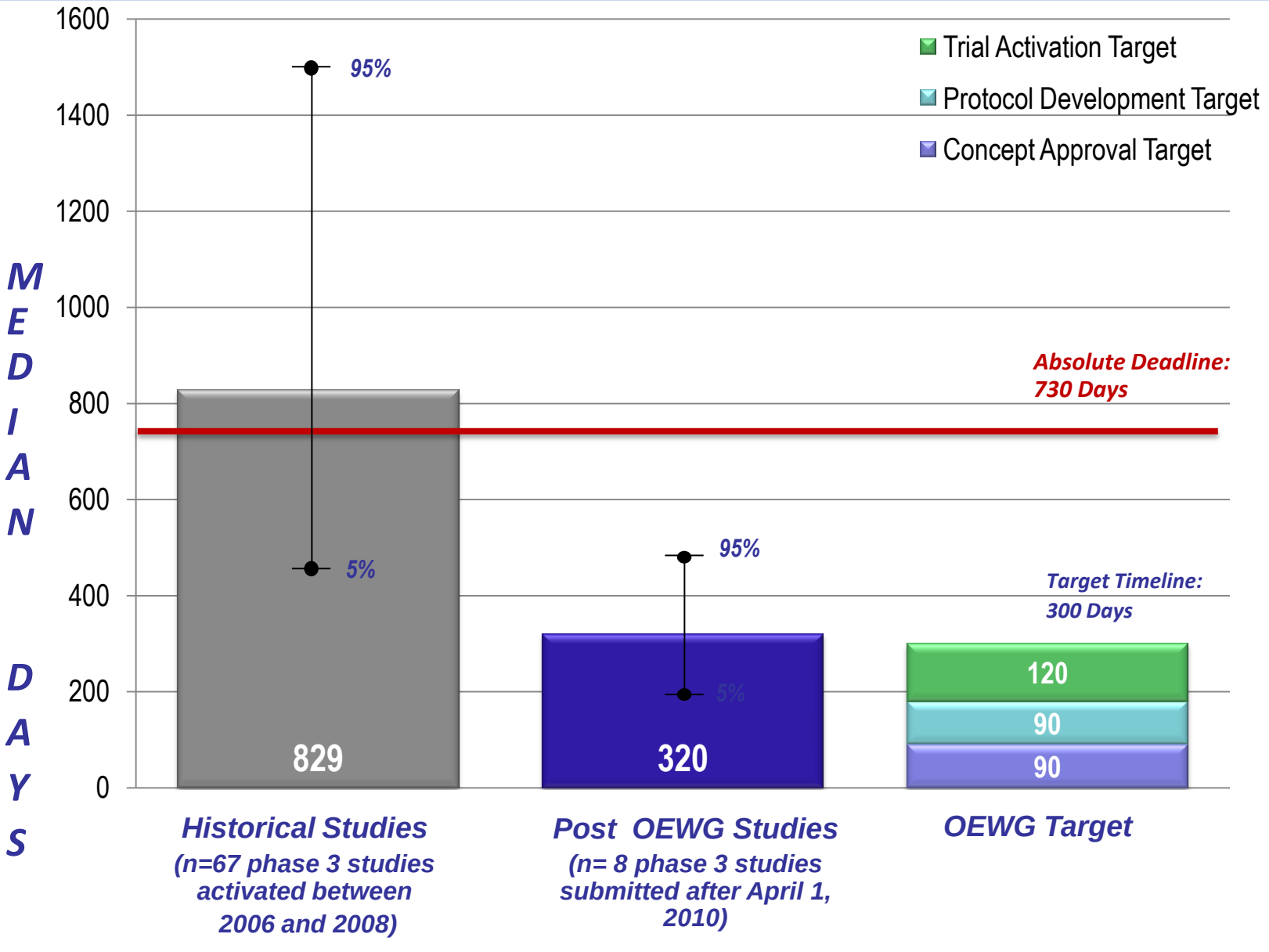
Timeline Comparison of Study Activation for Phase III Trials: Historical vs. Post-OEWG (Apr 2010 – May 2012)



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***

Current as of 04/30/2012

Study Assessing CIRB Costs

- **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*

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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**

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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***

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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

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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

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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

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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

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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

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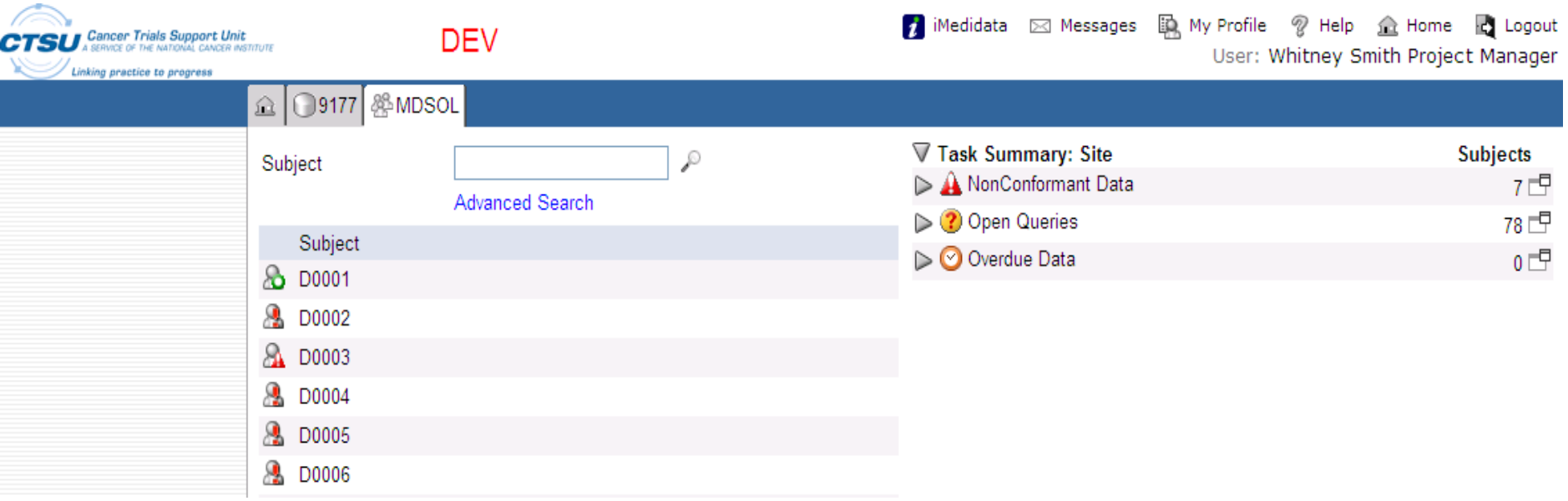
The Vision for a Common CDMS

Re-enforce focus on <u>Science and the Patient</u>

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



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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)

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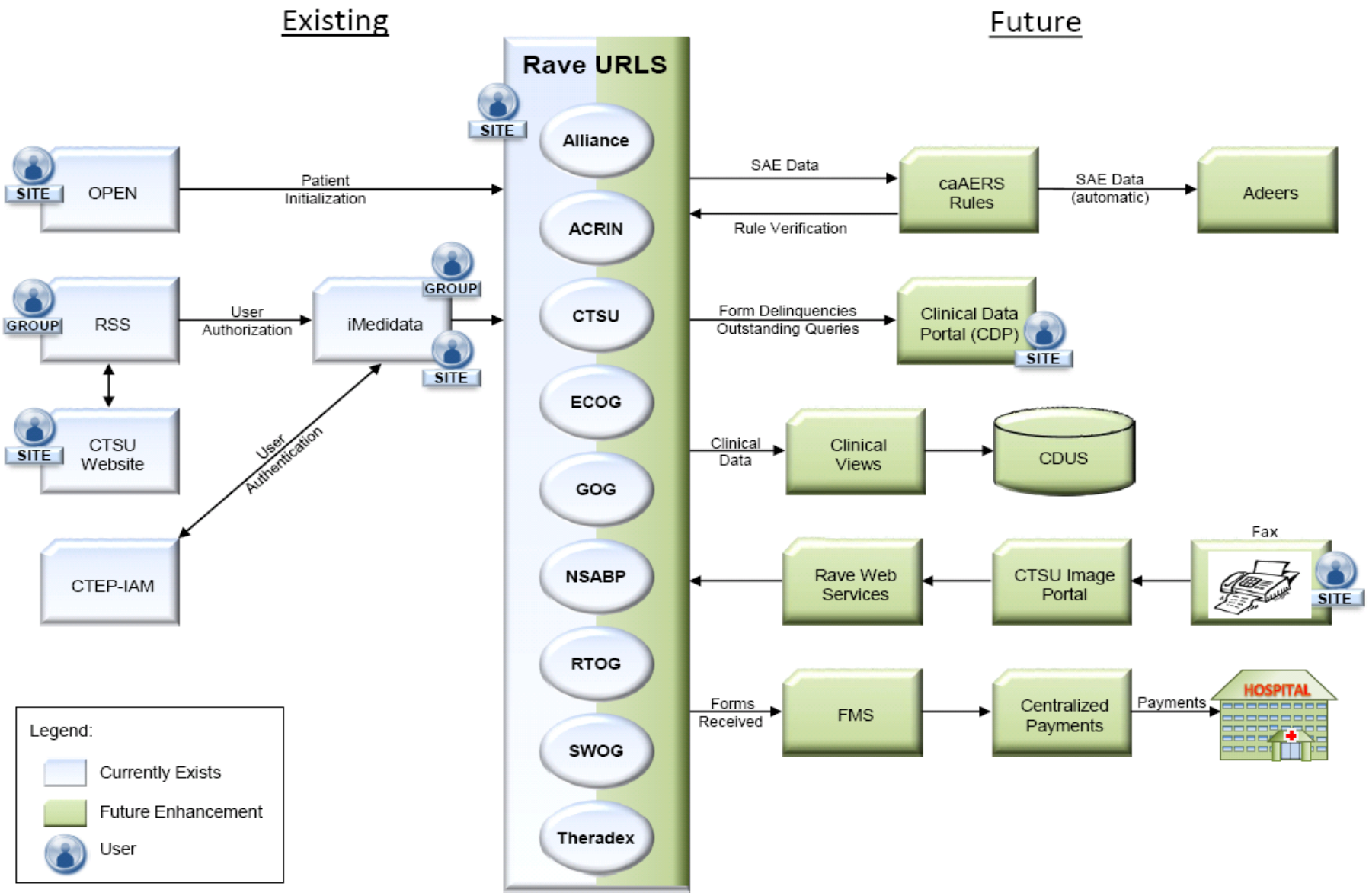
Key Concepts for Successful Deployment

- 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

Existing and Future Integrations



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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

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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

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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

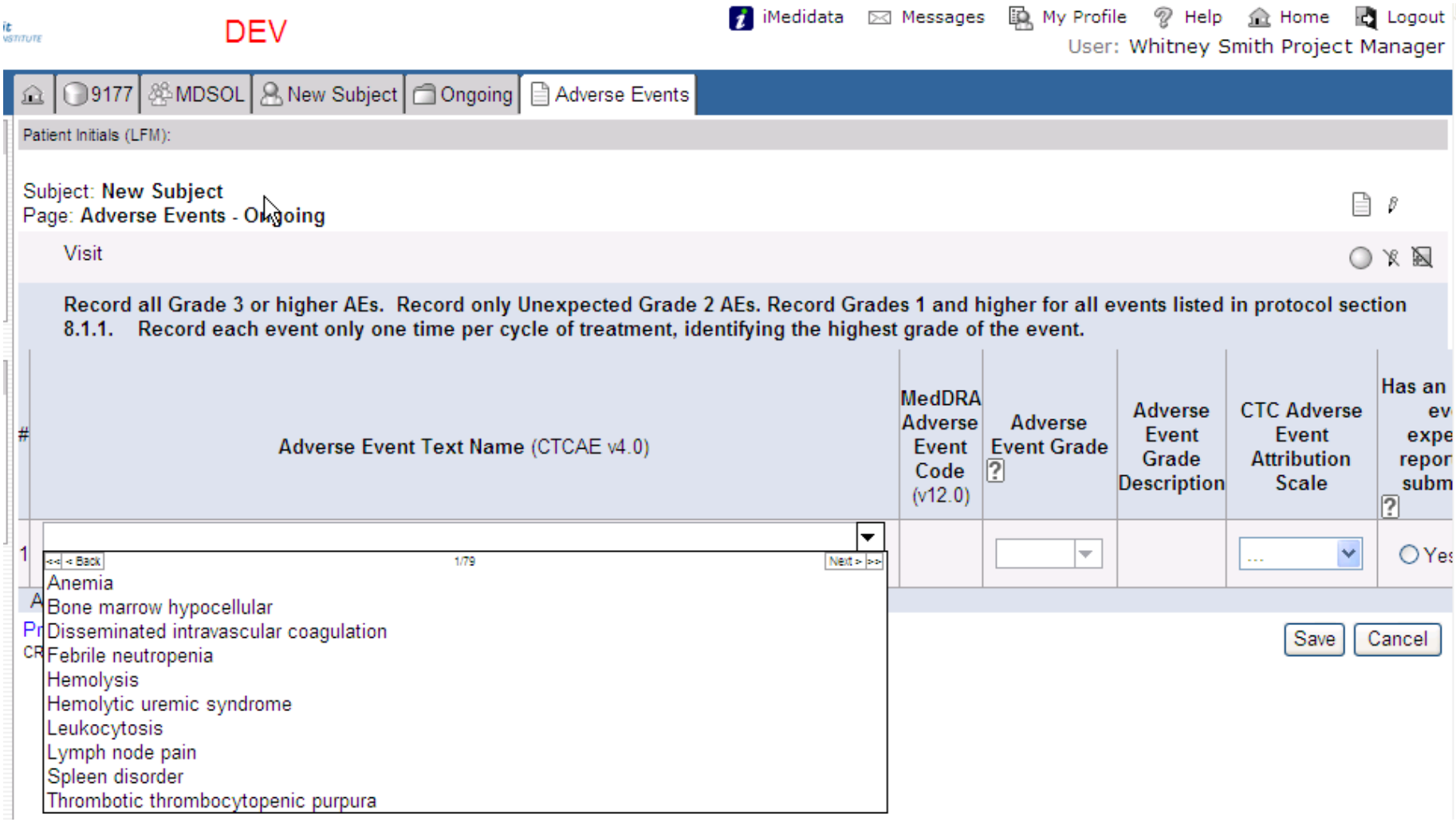
- Start Jul 1, 2011
- Second 3 sites (**Bravo**) begin deployment (start of stage)
  - 9-months to implement
- Alpha sites continue deployment activities

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



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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

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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**
- **NCI Central Institutional Review Board (CIRB)**
- **Electronic data capture and management system**