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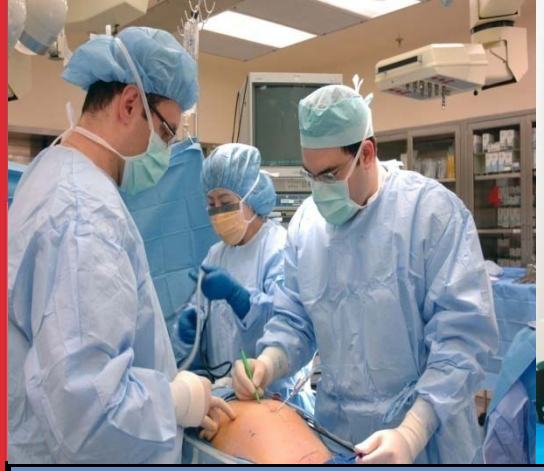

Institute of Medicine Report on a National Clinical Trials System for the 21st Century:

NCI Perspective and Current Activities

James H. Doroshow, M.D.
Division of Cancer Treatment and Diagnosis, NCI

IOM and ASCO Workshop
March 21, 2011

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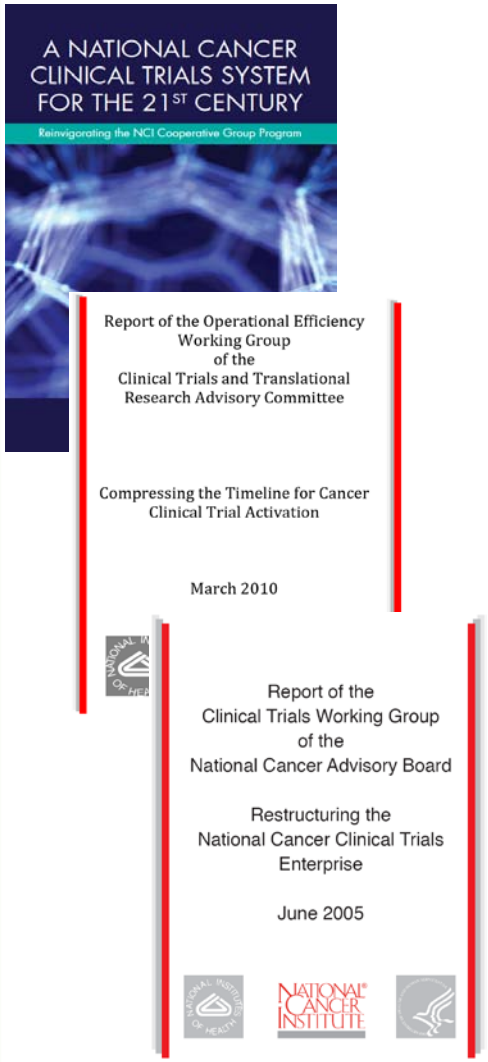
Institute of Medicine Report



Emphasized need for public clinical trials system

Four goals for modernization: 12 recommendations

- Improve speed & efficiency of trial development & activation
- Incorporate innovative science and trial design
- Improve prioritization, support, and completion of trials
- Incentivize participation of patients and physicians

NCI is implementing a comprehensive approach to transforming its clinical trials system to create a highly integrated network that can address rapid advances in cancer biology based on:

- Recommendations from the IOM Report
- Previous reports (Clinical Trials & Operational Efficiency Working Groups)
- Current stakeholder input

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IOM Goal 1: Improve Speed and Efficiency of the Design, Launch, & Conduct of Clinical Trials

Recommendation 1

NCI should facilitate some consolidation of Cooperative Group "front-office" operations by reviewing and ranking the Groups with defined metrics on a similar timetable and by linking funding to review scores.

Progress

- As recommended by IOM, current focus on supporting up to 4 Adult Cooperative Groups with continued funding of 1 Pediatric Group
- Planning for NCI external peer-review of all Groups in same review cycle with new review criteria emphasizing collaboration and evaluating Groups as partners in a National Clinical Trials Network
- Engaged in on-going discussion with the Cooperative Group Chairs about potential consolidation activities with some Groups already taking first steps to consolidate (RTOG-NSABP; ACOSOG-CALGB-NCCTG; ECOG-ACRIN)

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Scientific Rationale for Transforming Current System

CLINICAL TRIALS NETWORK

- Requirements for molecular screening of large patient populations to define subgroups for study necessitates that NCI-supported clinical research groups function as a coordinated network
- Extramural scientific prioritization of the phase III portfolio across all disease entities essential to efficiently develop and complete multicenter trials; a smaller number of disease committees better suited to building consensus
- Currently configured Groups have disincentives to study less common diseases due to potential failure of disease committees in review for taking any risk in accrual; a major problem for one group (but not for a national network with dramatically changed review criteria)
- Shared IT infrastructure with common front end for clinical data management and for tissue resource management will constantly require modification—more manageable with fewer independent entities
- Open access to a national clinical trials network for clinical/translational investigators not currently involved in the current Group platform will assure the best competition of ideas and the movement of high priority science into the clinical trials arena

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Organizational Structure for the Future: Options (1)

- Single national group
  - Pro
    - ✓ Fully integrated
    - ✓ No operational overlap
    - ✓ Potentially easier to harmonize IT and biomarker studies
  - Con
    - ✓ Competition for ideas decreased with a single set of leaders
    - ✓ Scope of data management requirements exceeds capacity of academic infrastructures: Increased cost; loss of scientific personnel
    - ✓ Transferring all current group trials (> 100,000 pts under active treatment) to a new, single data coordinating center - a major, multi-year challenge
    - ✓ Loss of current volunteer support from investigators and community physicians tied to group identity

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Organizational Structure for the Future: Options (2)

- Network of (smaller number) of groups
  - Pro
    - ✓ Provides ample creative outlet for competition amongst best ideas
    - ✓ Facilitates close interactions between community and academic investigators; supports volunteerism, cost sharing, and philanthropic support
    - ✓ Permits continued involvement of scientifically integrated, data management organizations housed at academic sites – more affordable on a publicly supported budget
  - Con
    - ✓ Does not, by itself, guarantee coordinated approach across groups
    - ✓ Or, full integration across 'system'

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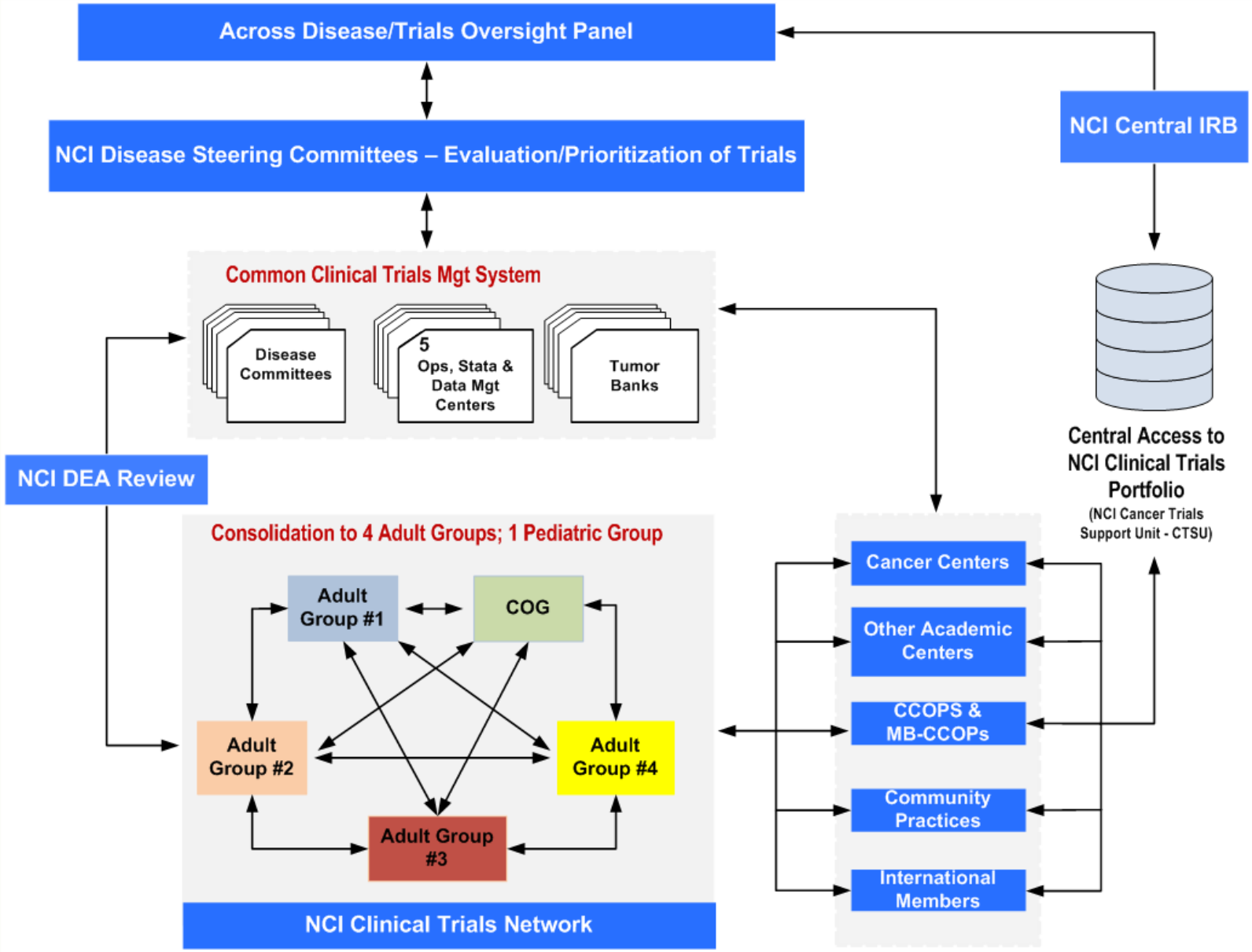
Proposed New Organizational Structure for the NCI's Clinical Trials Program



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IOM Goal 1: Improve Speed and Efficiency

Recommendation 2

Require/facilitate consolidation of Group "back-office" operations & working with extramural community, make process improvement in operations & organizational management a priority.

Progress

- Instituted comprehensive, centralized 24/7 patient registration for all Group trials, with regulatory and site verification of trial participation by the Cancer Trials Support Unit (CTSU)
- Implemented OEWG timelines for concept evaluation, protocol development, and trial activation
- Working with Groups on a single, harmonized approach to clinical trial management, including protocol authoring, case report forms, and standardized data collection & management

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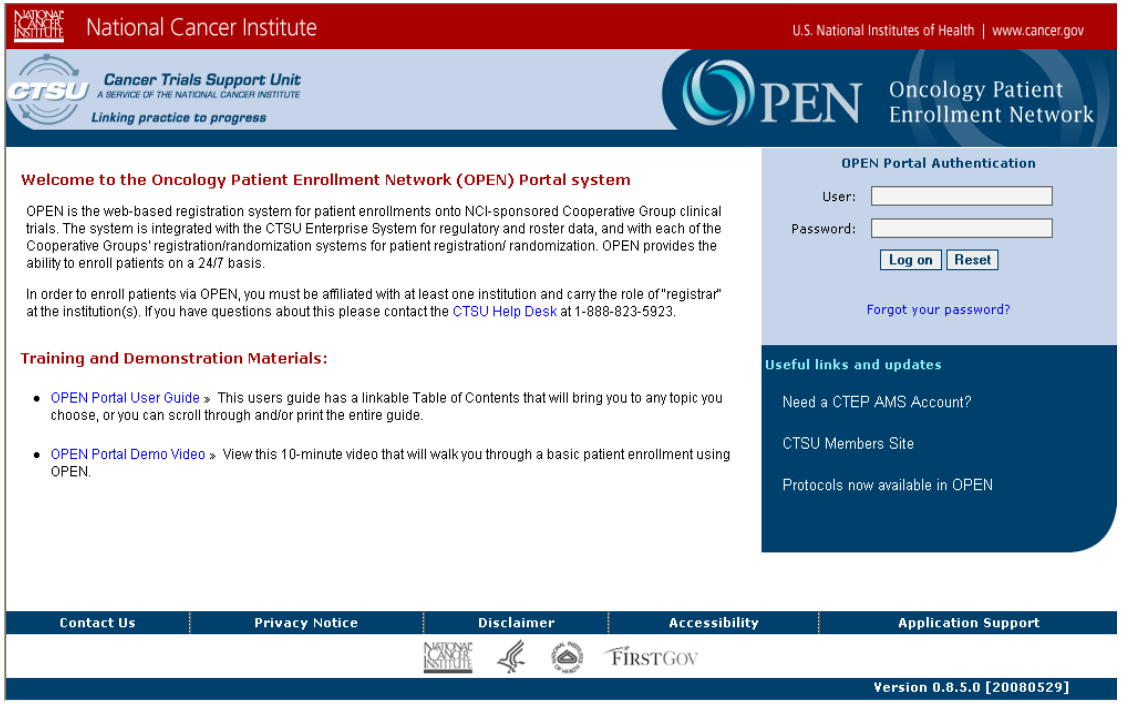
CTSU: A National Infrastructure for Patient Enrollment on NCI-Supported Clinical Trials

Cancer Trials Support Unit (CTSU) has expanded centralized administrative & regulatory functions for clinical trials:

- Over 48,000 patients enrolled via CTSU since 2002
- Cross-Group phase 3 trial accrual has increased from 20% to 40%
- Providing a range of critical services in support of the national system:
  - ✓ Patient registration
  - ✓ Accrual reimbursement
  - ✓ Protocol Coordination
  - ✓ Clinical Data Operations
  - ✓ Regulatory Support Services
  - ✓ Financial Management
  - ✓ Site Auditing
  - ✓ Site QA
  - ✓ CTSU Help Desk
  - ✓ CTSU Web Site
  - ✓ Education & Trial Promotion

As of 1/1/11, 24/7 enrollment for all Group Tx trials



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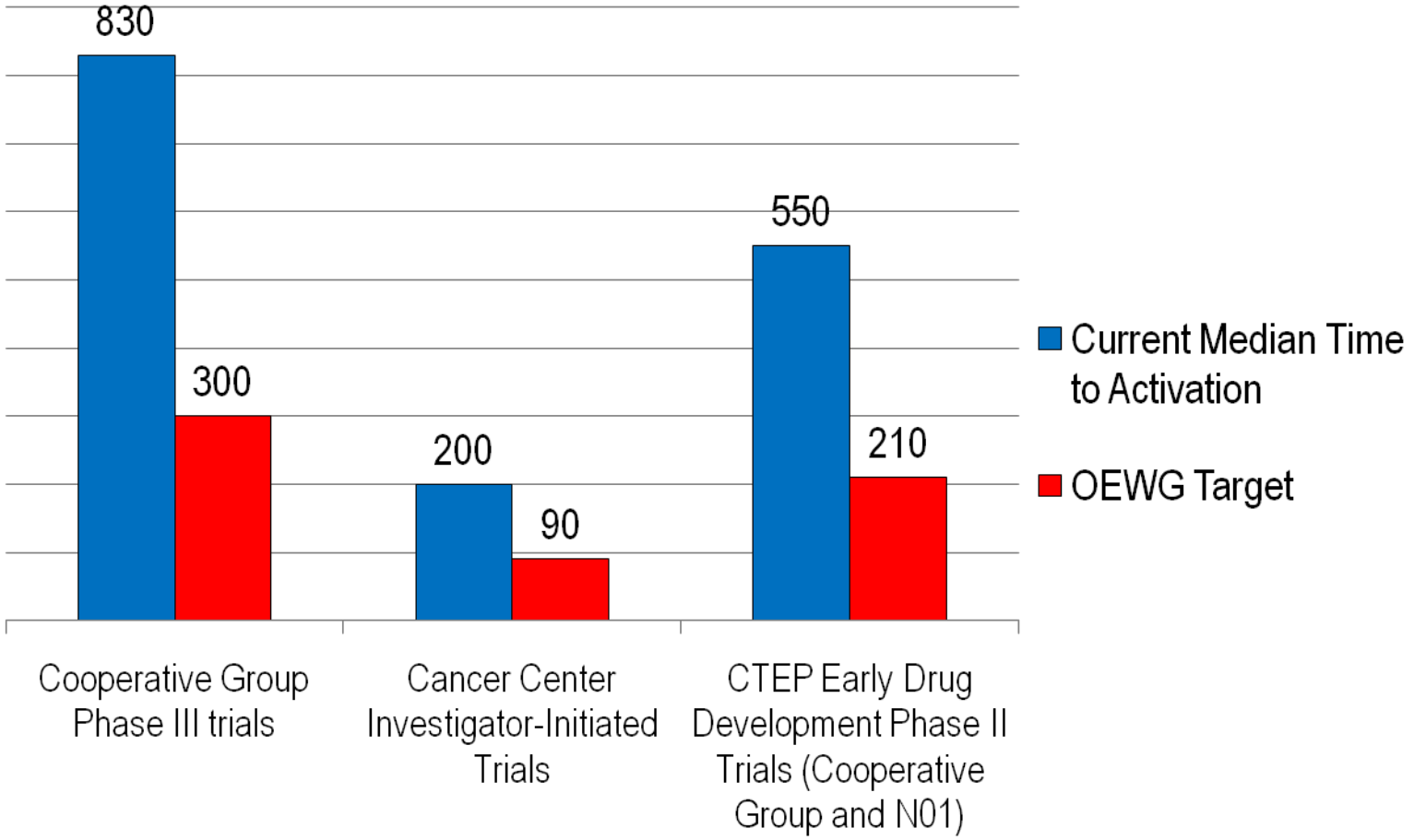
Operational Efficiency: Aggressive But Necessary New Targets



Current median time includes IRB approval, industry negotiations, and FDA approval

Phase 3 protocol development terminated if not activated in 2 years
Phase 2 protocol development terminated if not activated in 18 months

NCI Timeline Reports
CTEP Secure Website – Access/Login

Click here to access the secure website

Users with IAM accounts with the following roles on protocols will be able to access and view their protocols

- ***Principal Investigator***
- ***Site Coordinator***
- ***Investigator***
- ***Mail to Contact***
- ***Primary CDUS Contact***
- ***Secondary CDUS Contact***
- ***Grant Investigator***
- ***Grant PI***

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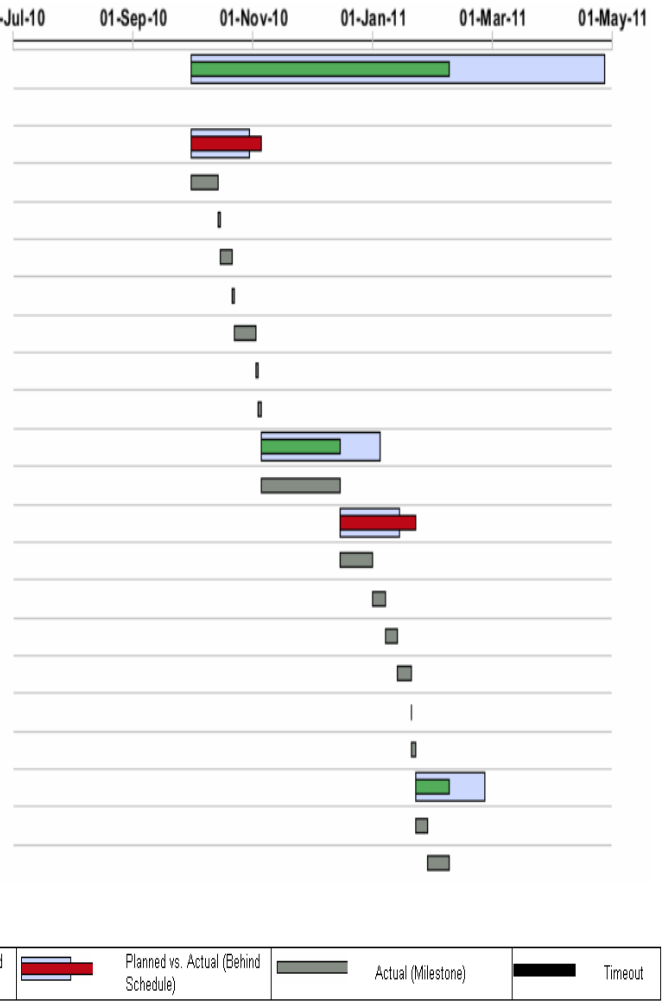
Providing Real Time Data To Improve Efficiency

OEWG Detailed Gantt Report

Document Number: 8976 **Pathway:** Unsolicited LOI's **Target Date:** 04/27/2011 **Absolute Deadline:** 03/22/2012 **Latest Activity (Date):**

Category / Stage Name / Milestone Name	Start Date	End Date	Duration
Overall Planned vs. Actual [Planned: 210 , Actual: 131 , Timeout: 0]	*09/29/2010*	*02/07/2011*	
LOI Approval - Initial LOI Consensus Evaluation [Planned: 30, Actual: 36]	**09/29/2010**	**11/04/2010**	**36**
OEWG Start Date to IDB Review	09/29/2010	10/13/2010	14
IDB Review to PRC Review	10/13/2010	10/14/2010	1
PRC Review to IDB Review	10/14/2010	10/20/2010	6
IDB Review to IDB Review	10/20/2010	10/21/2010	1
IDB Review to Conference Call - Planned	10/21/2010	11/01/2010	11
Conference Call - Planned to Consensus Review Completed (LOI)	11/01/2010	11/02/2010	1
Consensus Review Completed (LOI) to LOI Approved	11/02/2010	11/04/2010	2
Protocol Authoring - Protocol Development [Planned: 60, Actual: 40]	**11/04/2010**	**12/14/2010**	**40**
LOI Approved to Protocol Receipt	11/04/2010	12/14/2010	40
Protocol Development - Initial Protocol Consensus Evaluation [Planned: 30, Actual: 38]	**12/14/2010**	**01/21/2011**	**38**
Protocol Receipt to PRC Review	12/14/2010	12/30/2010	16
PRC Review to PRC Review	12/30/2010	01/06/2011	7
PRC Review to Consensus Review Received in PIO	01/06/2011	01/12/2011	6
Consensus Review Received in PIO to Consensus Review Completed	01/12/2011	01/19/2011	7
Consensus Review Completed to Consensus Review Sent to PI	01/19/2011	01/19/2011	0
Consensus Review Sent to PI to Conference Call - Planned	01/19/2011	01/21/2011	2
Protocol Development - Follow-Up Protocol Consensus Evaluations [Planned: 35, Actual: 17]	**01/21/2011**	**02/07/2011**	**17**
Conference Call - Planned to Revised Protocol Submitted	01/21/2011	01/27/2011	6
Revised Protocol Submitted to Protocol Approved On Hold	01/27/2011	02/07/2011	11



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Phase III Concepts: Timeline Data as of March 14, 2010

15 Concepts proposing Phase III Trials received since April 1, 2010

- 5 concepts approved
- 1 concepts in review or in time-out (company &/or drug commitment)
- 8 concepts disapproved or withdrawn
- 1 concept submitted to CTEP awaiting Steering Cmte. Review

Approved Phase III Concepts (5):

Target timeline for Phase III concept receipt to approval = 90 days

- Average number of days for Phase III concept approval by Steering Cmte. (subtracting out the time-outs) = 89.5 days (2 studies)
- Average number of days for ph III concept approval w/o SC (subtracting out the time-outs) = 46 days (3 studies)

Protocols (3):

Target for Phase III concept approval to protocol submission = 90 days

- Average number of days for Phase III protocol submission = 79 days

Target for Phase III concept approval to protocol activation = 210 days

- Average number of days for Phase III protocol activation= 199 days (1 study)

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IOM Goal 1: Improve Speed and Efficiency

Recommendation 3

HHS should lead a trans-agency effort to streamline and harmonize government oversight and regulation of cancer clinical trials.

Progress

- Established an interagency agreement with FDA for early review of approved Cooperative Group phase 3 treatment trials. This allows for rapid 21-day review of a concept if it has been identified as a licensing trial
- Developed coordinated protocol development & review processes with Groups for phase 3 trials developed under FDA Special Protocol Assessment (SPA)
- Developed adult & pediatric NCI Central IRB with OHRP for Group trials w/ recent major improvement in review timelines & plan for AAHRP accreditation
- Working with CDRH/FDA to coordinate early review of investigational devices used in treatment trials (biomarker assays, genomic signatures)

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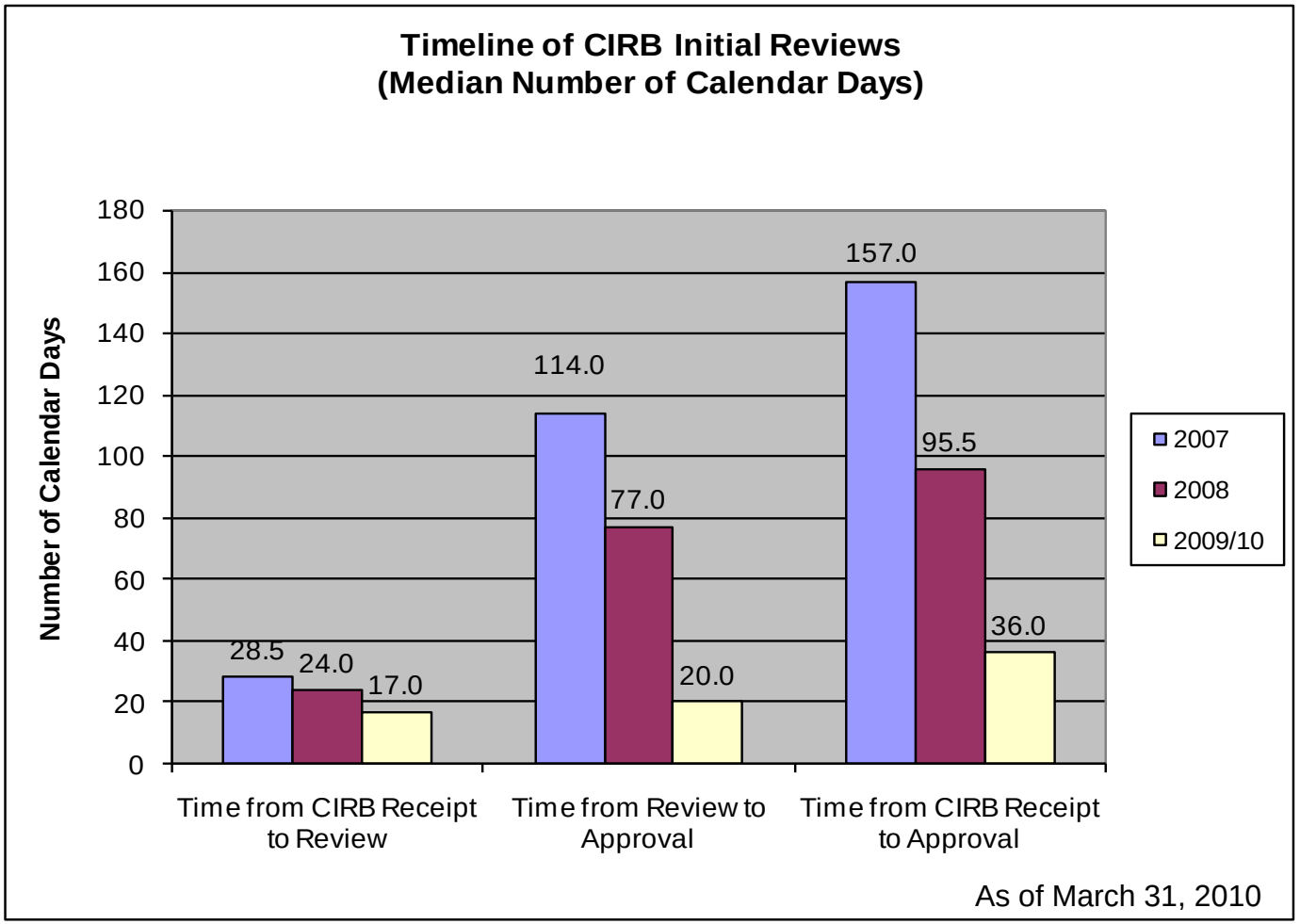
CIRB: Changes in Initial Review Timeline



Updated Statistics:

Average Time from CIRB Receipt to Approval from January 1, 2010 to March 10, 2011 was 37 Days for Adult Phase 3 Trials

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IOM Goal 2: Incorporate Innovative Science and Trial Design Into Cancer Clinical Trials

Recommendation 6

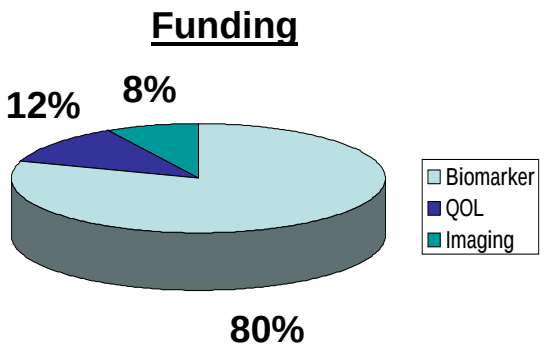
Cooperative Groups should lead the development and assessment of innovative designs for clinical trials that evaluate cancer therapeutics and biomarkers (including combinations of therapies).

Progress

•Initiated the Biomarker, Imaging, and Quality of Life Studies Funding Program to ensure that critical correlative studies could be incorporated in a timely manner into phase 3 and large, multi-institutional phase 2 trials during the process of concept development

• From mid-2008-2010, 14 of 40 concepts incorporating predominantly integral (some integrated) markers supported for a total commitment to date of $ 22,460,000.

• COG: AAML0531 Biomarkers: FLT3/ITD high allelic ratio (Integral) & CEBPα (Integrated) completed (>1000 pts)



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BIQSFP Applications for Group Phase 3 Treatment Trials Approved for Funding

- CALGB-30801: Phase 3 Double Blind Trial Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced NSCLC *(Integral & Integrated Markers)*
- RTOG-1010: Phase 3 Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma *(Integral Marker)*
- COG - AAML1031: A Phase 3 Randomized Trial for Patients with de novo AML using Bortezomib and Sorafenib for patients with FLT3 ITD *(Integral & Integrated Markers)*
- S1007: A Phase 3 Randomized Clinical Trial of Standard Adjuvant EndocrineTherapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone-responsive and HER2-negative Breast Cancer According to Recurrence Score *(Integral Marker)*

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IOM Goal 2: Incorporate Innovative Science and Trial Design Into Cancer Clinical Trials

Recommendation 6

Cooperative Groups should lead the development and assessment of innovative designs for clinical trials that evaluate cancer therapeutics and biomarkers (including combinations of therapies).

Progress (contd.)

- Worked with Investigational Drug Steering Committee on evaluation of innovative clinical trial designs as well as other key issues related to cancer therapeutics:
  - ✓ "Design of phase II clinical trials testing cancer therapeutics: consensus recommendations from the clinical trial design task force of the NCI investigational drug steering committee. Clin. Cancer Res. 16: 1764-1769, 2010
  - ✓ "Novel designs and endpoints for phase II clinical trials. Clin. Cancer Res. 15: 1866-1872, 2009
  - ✓ "Approaches to phase I clinial trial design focused on safety, efficiency, and selected patient populations: a report from the clinical trial design task force of the NCI investigational drug steering committee. Clin. Cancer Res. 16: 1726-1736, 2010

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IOM Goal 3: Improve Prioritization, Selection, Support, and Completion of Cancer Clinical Trials

Recommendation 8

NCI should re-evaluate its role in the clinical trials system.

Progress

- Initiated Clinical Trials and Translational Research Advisory Committee: First Federally-chartered NCI advisory group in a decade; in operation for >3 years with specific responsibilities for NCI's clinical trials programs; currently engaged in evaluation of implementation of CTWG recommendations; developing under CTAC guidance an extramural group to provide strategic input for clinical trials network
- Revamped prioritization process for large phase 2 and phase 3 treatment and control trials by creating disease- and modality-specific Steering Committees to ensure that most important trials are given highest priority

--While NCI has a voice on the Steering Committees, its role is to facilitate trial implementation, rather than to direct the primary review

--Steering Committees convene clinical trials planning meetings to identify critical clinical trial issues for future studies

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Disease-Specific Steering Committees: Prioritizing Clinical Trials

Steering Committee	Year Established	Co-Chairs Disease-Specific Steering Committees (SCs)
GI	2006	Dan Haller, MD & Joel Tepper, MD
Gyne	2006	David M. Gershenson, MD, Gillian Thomas, MD, & Michael Birrer, MD
Head & Neck	2007	David Adelstein, MD, David Brizel, , MD, & David Schuller, MD
GU	2008	Eric Klein, MD, George Wilding, MD*, & Anthony Zietman, MD
Breast	2008	Charles Geyer, MD & Nancy Davidson, MD*
Thoracic	2008	David Harpole, MD, William Sause, MD, & Mark Socinski, MD
Leukemia	2009	Wendy Stock, MD & Jerry Radich, MD
Lymphoma	2009	Oliver Press, MD & Julie Vose, MD
Myeloma	2009	Morie Gertz, MD & Nikhil Munshi, MD
Brain	2010	Ian Pollack, MD & Al Yung, MD
Pediatrics (Heme & Solid Tumors)	2011	David Poplack, MD (Leukemia & Lymphoma) Mark Bernstein, MD (Solid Tumors)

Over 140 Concepts evaluated since inception of SCs

*Cancer Center Directors

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Other Related Steering Committees: (Non-disease Focus)

- Investigational Drug Steering Committee
  - Co-Chairs: Pat LoRusso, DO, & Dan Sullivan, MD
- Clinical Imaging Steering Committee
  - Co-Chairs: Steven Larson, MD and Etta Pisano, MD
- Symptom Management & Health-Related Quality of Life Steering Committee
  - Co-Chairs: Deborah Bruner, RN, PhD & Michael J. Fisch, MD, MPH
- Patient Advocate Steering Committee
  - Co-Chairs: Regina Vidaver & Nancy Roach

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IOM Goal 3: Improve Prioritization, Selection, Support, and Completion of Cancer Clinical Trials

Recommendation 9

NCI, Groups, and physicians should take steps to increase the speed, volume, and diversity of patient accrual and to ensure high-quality performance at all sites participating in Group trials.

Progress

- Modernizing the clinical trials IT infrastructure by procuring a clinical trials data management system that can be used across the NCI-supported Cooperative Group System
- Enhancing trial participant diversity through support for Minority-based Community Clinical Oncology Programs, Patient Navigator Research Program, and other NCI programs
- Working with patient advocates in concept development and accrual planning, along with Cooperative Groups, Disease Steering Committees, and Patient Advocate Steering Committee

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IOM Goal 3: Improve Prioritization, Selection, Support, and Completion of Cancer Clinical Trials

Recommendation 10

NCI should allocate a larger portion of its research portfolio to the Clinical Trial Cooperative Group Program to ensure that the Program has sufficient resources to achieve its unique mission.

Progress

- NCI developed targeted initiatives that have increased reimbursement to sites from $2,000 to $5,000 per enrolled patient for large phase 2 studies; and additional funding provided for select phase 3 trials based on complexity; as well as the funding for critical biomarker, imaging & QOL studies
- However, without an increase in resources, changes in the funding model must be considered in the context of the number of new trials, the total accrual that can be sustained, and the need for supporting correlative science
  - ✓ Focus on high-accruing organizations (~80% accrual from ~50% major sites)
  - ✓ Need for additional infrastructure support
  - ✓ Currently being discussed with Cooperative Group Chairs

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IOM Goal 4: Incentivize the Participation of Patients and Physicians in Clinical Trials

Recommendation 11

All stakeholders should work to ensure that clinical investigators have adequate training and mentoring, paid protected research time, the necessary resources, and recognition.

Progress

- NCI created the Clinical Investigator Team Leadership Award to promote collaborative science and recognize outstanding clinical investigators; the first awards were made in 2009

New award to acknowledge & fund those who lead clinical cancer research programs at NCI-Designated Cancer Centers: 2010 Awardees

Dr. Rafat Abonour, Indiana University Melvin & Bren Simon Cancer Center
Dr. Jeffrey Bradley, Siteman Cancer Center
Dr. Steven Cohen, Fox Chase Cancer Center
Dr. Linda Duska, University of Virginia Cancer Center
Dr. Naomi Haas, Abramson Cancer Center
Dr. Elisabeth Heath, The Barbara Ann Karmanos Cancer Institute
Dr. Susan Kelly, The University of Texas M. D. Anderson Cancer Center
Dr. Smitha Krishnamurthi, Case Comprehensive Cancer Center
Dr. Suresh Ramalingam, Winship Cancer Institute
Dr. David Rizzieri, Duke Comprehensive Cancer Center
Dr. Cheryl Saenz, Moores Cancer Center
Dr. Sheri Spunt, St. Jude Children's Research Hospital

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Developing A National Clinical Trials Network: An On-going Process

- Work with Groups and critical stakeholders: Current Cooperative Group PIs, CCOP PIs, ASCO, AACR, Cancer Centers, other professional groups & advocates to develop consensus
  - CTAC discussion: Dec 15, 2010; March, 2011
  - Discuss with members of IOM panel; one-to-one calls December 2010
  - Meetings with Group Chairs: 11/29; 1/11; 2/11; 3/11; 4/11; 5/11; 6/11
- Provide opportunity for public comment
  - NCI website (http://transformingtrials.cancer.gov)
  - Meetings with professional societies, advocates, IOM
- Modify initial recommendations based on feedback
- As new configuration for the Group program is developed:
  - Timetable for implementation
  - New FOA for an NCI Clinical Trials Network
  - New review criteria and guidelines
  - Present to NCAB, BSA, CTAC, Cancer Center Directors
- Pursue CTAC Subcommittee Evaluation Plan: System Performance/Outcomes, Collaboration, Disease Steering Committees
- Simultaneously advance ongoing work on other issues raised by IOM: tissue banks, funding, efficiency, coordination, correlative science, etc.

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Additional Slides

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Implementation of IOM Report by NCI: Other Recommendations

Recommendation 4

NCI should take steps to facilitate more collaboration among the various stakeholders in cancer clinical trials.

Recommendation 5

NCI should mandate submission of annotated biospecimens to high-quality, standardized central biorepositories when samples are collected from patients in the course of Group trials and should implement new funding mechanisms and policies to support the management and use of those resources for retrospective correlative science.

Recommendation 7

NCI, in cooperation with other agencies, should establish a consistent, dynamic process to oversee development of national unified standards.

Recommendation 12

Health care payment policies should value the care provided to patients in clinical trials and adequately compensate that care.

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IOM Goal 1: Improve Speed and Efficiency

Recommendation 4

NCI should take steps to facilitate more collaboration among the various stakeholders in cancer clinical trials.

Progress

- NCI is working across divisions to harmonize guidelines for programs engaged in the conduct of clinical trials so that the appropriate incentives are in place for collaboration (SPORES, Cancer Centers, Groups)
- In collaboration with CEO Roundtable on Cancer, developed Standard Terms of Agreement for Research Trials (START) clauses for company and academic collaborations; speeded clinical trial negotiations
- Assessing feasibility of developing standardized Material Transfer Agreements (MTAs) that cover IP considerations for industry and academic institutions
- Revised IP option on all CTEP Cooperative Research and Development Agreements (CRADAs) relating to drug development and specimen/correlative science interactions; published in Federal Register March 11, 2011 (CTEP Intellectual Property Option to Collaborator; Pages 13404-13410 [FR DOC# 2011-5609])

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IOM Goal 2: Incorporate Innovative Science and Trial Design Into Cancer Clinical Trials

Recommendation 5

NCI should mandate submission of annotated biospecimens to high-quality, standardized central biorepositories when samples are collected from patients in the course of Group trials and should implement new funding mechanisms and policies to support the management and use of those resources for retrospective correlative science.

Progress

- Revising RFA for U24 grants for National Specimen Banks to include common operating procedures for samples collected from patients enrolled in Group (and other) NCI-supported trials & reflecting consolidation of the Group system
- Working with Groups to develop a common review process & procedures for requests for biospecimens banked from clinical trials
- Need to develop shared IT infrastructure to enhance specimen inventories

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IOM Goal 2: Incorporate Innovative Science and Trial Design Into Cancer Clinical Trials

Recommendation 7

NCI, in cooperation with other agencies, should establish a consistent, dynamic process to oversee development of national unified standards.

Progress

- Under auspices of the Clinical and Translational Research Advisory Committee, developed definitions of integral and integrated studies for biomarkers, imaging, and quality of life investigations associated with Group Trials, and priorities for support thereof
- Working with the NLM and the AACI to develop the Cancer Trials Reporting Program database to provide accrual information related to all NCI-supported clinical trials

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IOM Goal 4: Incentivize the Participation of Patients and Physicians in Clinical Trials

Recommendation 12

Health care payment policies should value the care provided to patients in clinical trials and adequately compensate that care.

Progress

- Worked with Centers for Medicare & Medicaid Services (CMS) to establish pilot program for reimbursement for clinical trials care under a CMS national coverage decision for agents used for colorectal cancer as well as on data collection to evaluate use of imaging and other clinical modalities
- Leading new CMS interagency (NIH-FDA-CMS) work groups to assist in the development of approaches to reimbursement for genetic tests used to choose targeted therapy and for the use of helical CT for lung cancer screening