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Transforming the NCI's Clinical Trials System

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Structural & Organizational Approaches to Transforming NCI's Clinical Trials Program

Goal: a national clinical trials network comprised of Cooperative Groups interacting to co-develop, co-implement and co-conduct innovative & practice-changing trials to improve the nation's cancer care

- **Overarching assumptions and rationale for change**
- **How many Groups should there be?**
- **What are we recommending for new organizing principles and NCI peer-review of the program?**
- **What will a national clinical trials network look like when change occurs?**

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Assumptions Underlying Change

- Role of an NCI-supported national clinical trials system is to design, conduct, and rapidly complete large, randomized, multi-site Phase 2 and Phase 3 clinical trials of the highest scientific priority for treatment, control, screening, diagnosis and prevention

- Implement a comprehensive approach to change that acknowledges the IOM recommendations, but fundamentally alters current incentives at all levels to catalyze the formation of a highly integrated, national clinical trials network

- Rely on a more precisely-focused NCI (DEA, Division of Extramural Activities) peer-review system to stimulate and maintain transformative change

- Substantial operational, management, and cultural change by the Groups, NCI, and the clinical trials community will justify additional investment in the system

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Scientific Rationale for Transforming Current System

GROUP CONSOLIDATION

- Ability to prioritize molecular characterization resources, and develop molecularly-driven trial designs is critical for future success of multisite clinical trials; this can be achieved more easily with fewer competing research organizations
- Extramural scientific prioritization of the phase III portfolio across all disease entities is essential to efficiently develop and complete multicenter trials; a smaller number of competitive Group disease committees is 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

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Scientific Rationale for Transforming Current System (cont'd)

CREATING A NETWORK

- Requirements for molecular screening of large patient populations to define subgroups appropriate for study necessitates that NCI-supported clinical research groups function as a coordinated network
- Scientific interactions around imaging are facilitated by integrating ACRIN into a setting with more access to patient resources for investigational studies
- Harmonize procedures for scientific/administrative oversight for quality of life/cancer control and therapeutic trials between the Divisions of Cancer Prevention and Cancer Treatment and Diagnosis
- Optimal use of crucial tissue specimens from NCI-supported prospective trials difficult due to lack of national IT tissue locator resource, standard SOPs, and a transparent process to prioritize the distribution of specimens on a national scale
- 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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What are the Metrics/Endpoints for Success?

- System not only provides essential infrastructure for majority of Cooperative Group trials in treatment, control, screening, diagnosis, and prevention; but is major enabler of cutting-edge translational investigation across all of NCI's clinical research programs

- System opens trials rapidly that are approved by steering committees and completes accrual according to defined guidelines by leveraging an integrated national network of performance sites

- System provides a unified clinical and translational infrastructure for the extramural cancer community: investigators, patients, advocates, and industry

- New system at forefront of translational oncologic discovery; efficiently functions to answer critical questions not well supported in a commercial environment

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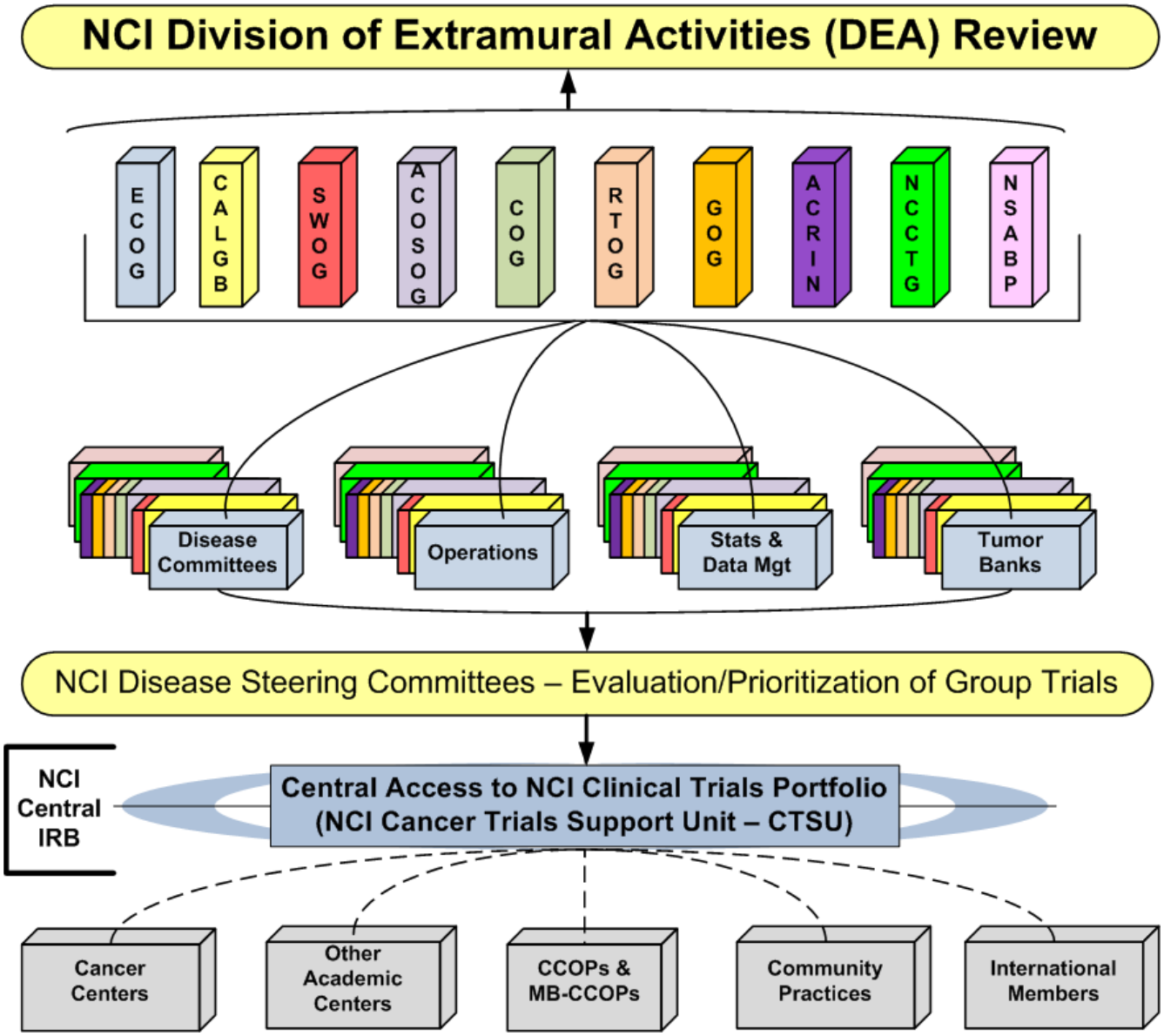
Organizational Structure of the Program: 2010



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How Many Groups Should There Be?

- Maintenance of a nationwide system of investigators at academic and community sites assures the most rapid and effective transfer of new treatment, control and prevention discoveries to patients
  - A few large groups would meet the needs of investigators for training, education, and adoption of new discoveries
- Several multi-disease Adult Groups (not to exceed 4) should provide ample creative outlets for disease leaders across the nation
  - Most advanced, adult diseases are still incurable. A few Adult Groups, as opposed to only one or two, should promote competition for the best trial ideas
  - While these Groups can focus their research on different cancers, they should all be capable of performing multi-disciplinary trials across the spectrum of cancer treatment, control, diagnosis, screening and prevention
- The four Pediatric clinical trials groups were merged previously into one entity (COG); it should remain

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What Are We Recommending?

- Integration into not more than 4 Adult Groups with multi-modality capacity in a broad range of diseases all fully committed to a national clinical trials system

- Potential strategies to assist integration:
  - NIH grants now permit multiple PIs which may help with the leadership transition
  - Incentivize the transition with provision of additional resources
  - Allow a distributed data management and operations system to avoid disruption of ongoing trials
  - Combine (rather than disband) overlapping disease committees to include all current participants

- Re-configuring NCI review of the NCI's clinical trials program with emphasis on incentives for a national system

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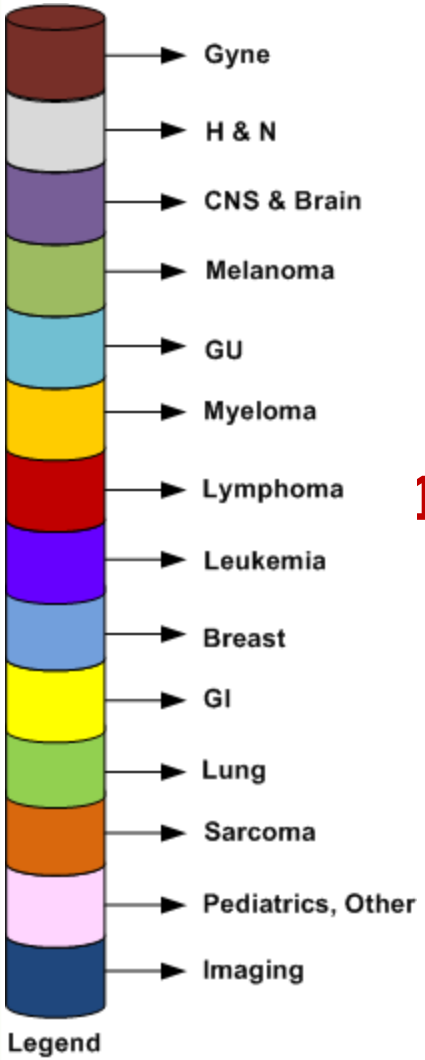
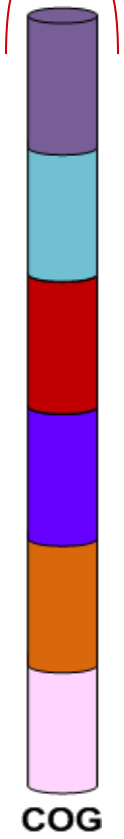
Proposed New Organizational Structure

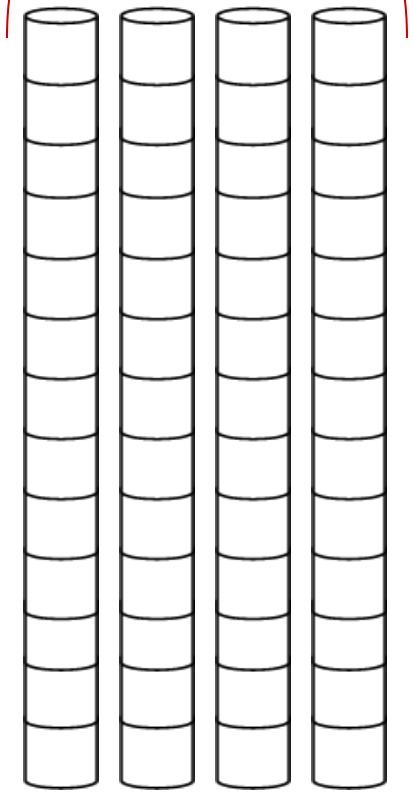


Merging 10 Groups to 5

1 Pediatric Group



4 Adult Groups



Diseases (colors) to be decided based on integration of specific Group disease committees

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Outcome of Adult Group Integration

- 4 (harmonized) Operations Centers instead of 9
- 4 (harmonized) Data Mgt Centers instead of 9
- Maximum of 4 Disease-Specific Committees/cancer type instead of up to 8
- 4 Coop Group Cancer Control/Prevention Research Bases instead of 8
- 3 Tumor Banks instead of 9

Simplifies Harmonization of System

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Outcome of Group Integration (cont'd)

A networked system is better able to perform studies:

- In less common malignancies
- Requiring sophisticated imaging modalities
- Necessitating rapid molecular characterization of tumors
- Involving access to a nationally integrated tissue resources
- Initiated (idea generated) by investigators not now involved in current Group activities
- Prioritized across all diseases and modalities of care

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What is a Group in the New System?

- Groups will be fully integrated infrastructures that can go from idea generation and trial implementation to accrual and analysis (scientific committees, operations offices, membership, data management, statistics, and tumor bank resource)
- BUT, the current structure will be transformed to support a system that is functionally a network of groups with harmonized infrastructures and shared responsibilities:
  - Support for all concepts approved by steering committees regardless of their source
  - Study chairs assigned to every SC-approved study
  - Sharing of expertise and technology will be rewarded
  - Common practices for partnering with Industry and Philanthropy
  - Accrual reimbursement system that is equitable and transparent
  - Promotion of public access across system (tissue, clinical raw data)

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What is a Group in the new system? (cont'd)

- Idea generation can come from any Group as well as from investigators not affiliated with a Group
- Any Group can manage a trial whether or not it has a disease committee
- All Group phase III and certain phase II trials (approved by the SCs) go on the CTSU menu, and a co-chair is named, by each Group with a relevant disease committee
- Investigators can credit any Group they belong to and that Group will reimburse for that trial
- Group operations will be required to support and manage studies originated by investigators or investigator networks outside the Group, provided that the study is approved by Steering Committee review. Funds for this activity must be budgeted in new awards.

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Beneficial Effects of Scientific/Operational Unified Structure

<u>Maintenance of 4 Adult Groups with appropriately resourced infrastructures will allow preservation of NCI's long-term investment in the positive attributes of the current system</u>

- Maintains investigator volunteerism and participation in patient accrual through scientific engagement and commitment to shared mission
- Model of integrated, not-for-profit entities with distinctive histories and identities facilitates raising of non-NCI resources
- External funding, institutional cost-sharing and pro bono time enables a Phase 2-3 clinical trial program at relatively low cost to NCI
- Improves trial operations by facilitating close interaction among scientific and operational elements of protocol teams

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Risks of Consolidation of Adult Groups

- System currently depends to an important degree on investigator volunteerism – hence, infrastructure change involves risk
- Costs will increase (transition costs in short term) to harmonize operations (software/hardware) and committee structures
- Managing leadership issues among multiple Group PIs & committee co-chairs
- Change will require buy-in of multiple stakeholders:
  - Group board members
  - Group members
  - Broader scientific community; scientific societies
  - Industry
  - Patients and patient advocates

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New Organizing Principles for a National Clinical Trials Network

How do we effect the change needed to develop a new, national clinical trials network?

- Principles of Governance
- Critical Components of Review that Will Produce Desired Change
  - Evaluation of how well new clinical trials developed/completed: Scientific review of network components
  - Examination/review of how well the components of the clinical research infrastructure are integrated and managed
  - Review of the role each funded component plays in the effectiveness of the national system as a whole

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Governance: Challenge and Principles

Challenge: Fundamental transformation of a complex, goal-oriented clinical research enterprise requires new, shared strategic management

Principles:

- NCI & System (Group) leadership manage program as a collaborative national program to reach shared goals
  - Managed and reviewed not as separate "grants" but as components of an integrated system
  - "Cooperative Agreement" viewed by all not as a funding mechanism but as a way of doing business
- Recognition and support for the public-private nature of the funding structure requires shared NCI and Group decision-making
  - Cooperative Group awards
  - Group generated industry and philanthropic support
  - Investigator volunteerism and institutional cost sharing
- System managed & reviewed as both a scientific and an operational enterprise; will require major change in peer-review to incentivize performance of every component of new system

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Components of Review (1): Disease Steering Committees Manage Trial-Specific Review

- Trials from disease committees are currently prioritized by open process of scientific/clinical peer-review by a broad spectrum of experts (Scientific Steering Committees); NCI has a voice on these committees but its primary role is facilitative

- Current incentives must be refocused away from 'credit' to the Group for leading a trial; Steering Committees must focus exclusively on developing trials that will address the most important scientific question in a timely way

- Scientific Steering Committees & Groups need feedback and assistance in developing national clinical trial priorities; this will be provided by a cross-disease panel comprised of leadership from Extramural Scientists, Group Scientific & Statistical co-PI's, Steering Committee Chairs, advocates, and NCI; critical for development of strategic vision for new network

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Components of Review (2): Overview of NCI Peer Review

Reconfigured Peer Review for the New System

- The 4 newly configured adult groups and COG will undergo competitive review every 5 years coordinated by NCI's Division of Extramural Affairs

- Competitive review of the 5 Cooperative Groups will occur in the same year so that the Groups can be directly compared and resources allocated appropriately, based on the outcome

- Reviews will be shorter and limited to Group leadership only; Group scientific, statistical and operational leadership can defend the Group without participation by disease committee chairs

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Components of Review (3): Criteria for Scientific Evaluation

Review will no longer focus solely on trials put forward by specific disease committees; emphasis will shift to assessing the role of the Group as part of an integrated clinical trial system

- Accrual to trials of any Group in the relevant disease areas across the system
- Collaboration with other Groups & other NCI funded investigators, including combining trial concepts to design the most effective trials
- Leadership & participation in Steering Committees & Task Forces
- Number & quality of trial concepts proposed & trials approved over the full award cycle
- Design and leadership of Clinical Trials Planning Meetings
- Timely implementation and completion of trials, as well as analysis and dissemination of trial results
- Mentoring of young investigators to provide opportunities for them to develop concepts and lead trials
- IF the Group receives a passing score on the criteria above, the review committee will evaluate new treatment strategies for selected diseases (a few highlights - not comprehensive)

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Components of Review (4): Operational Efficiency

Review of Operational Efficiency of Infrastructures

- Implementation and maintenance of an integrated operational framework for operations office and data management functions within each Group
- Coordination and streamlining of operational processes
- Development and implementation of system-wide and Group-specific IT infrastructure and tools to enhance coordination and productivity
- Achievement of agreed upon timeline goals for each step in trial activation
- Achievement of target accrual goals for trials led by the Group as well as other, system-wide trials led by other Groups or components of the network
- Implementation of processes for effective trial oversight and response to safety issues
- Data quality as evidenced by audit results

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Components of Review (5): Review Criteria for Collaborative Management of the System as a Whole

<u>Groups will be reviewed on their contribution to the development & maintenance of a national, highly integrated clinical trials system</u>

- Active participation with NCI in collaborative management of overall Group Program
  - Identification of system-wide issues
  - Identification of management & operational best practices applicable across the system
  - Development of new cross-Group initiatives and/or policy/procedural changes
  - Demonstration of NCI-Group Liaison activities to solve problems and promote dialog
- Implementation of agreed upon improvements in operational and management policies and procedures
- Provision of clinical trial infrastructure resources for prioritized multicenter Phase 3 and 2 trials originated outside the Group
- Effective management of assigned cross-Group committees for rare diseases & implementation of prioritized trials in rare diseases

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CCOP Research Bases, CCOPs, and Tumor Banks

- CCOP research bases will be recompeted every 5 years at the same time, but on a different cycle from the treatment RFA
- CCOP RFAs will be annual with the ability for new CCOPs and recompeting CCOPs to submit
- The tumor bank U24 RFA will be recompeted on a different cycle from the treatment U10 RFA

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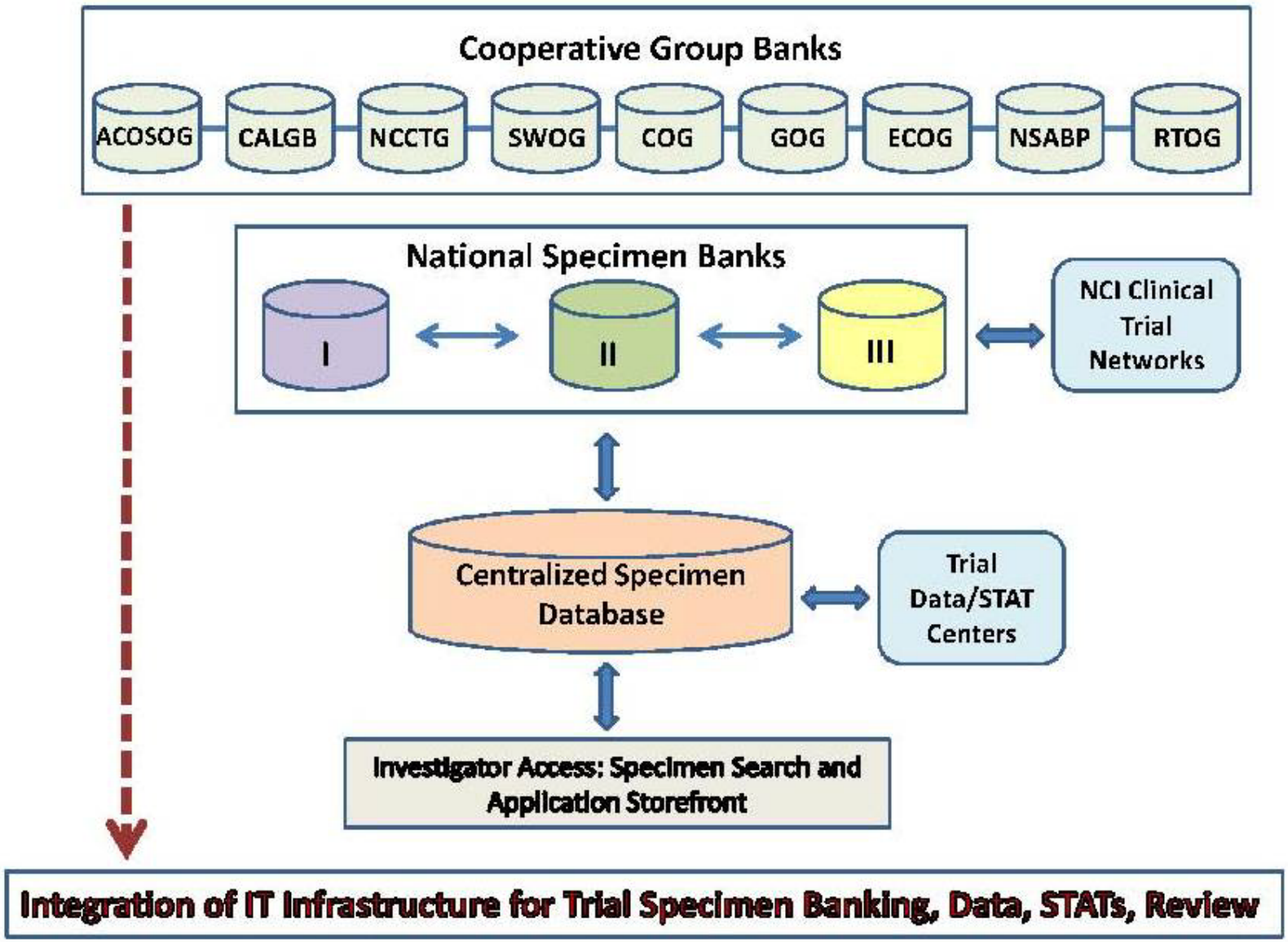
Reorganization of the National Specimen Banks



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Principles of Bank Reorganization

Banking Operations and Reorganization of Infrastructure:

- Prospective collection and storage of specimens on ongoing and future NCI clinical trials
- System for cataloguing and retrieval of "legacy specimens" and specimen-associated data
- IT tracking system connecting all banks
- IT connections between banks, STAT centers and NCI clinical trial system to retrieve de-identified specimen-associated data

Access to "Legacy" Specimens for the Research Community:

- Central inventory database of specimens available for research
- Centralized application and review processes
- Search engine for specimen retrieval

Provide transparent and uniform access to specimens for qualified investigators; current system difficult to navigate

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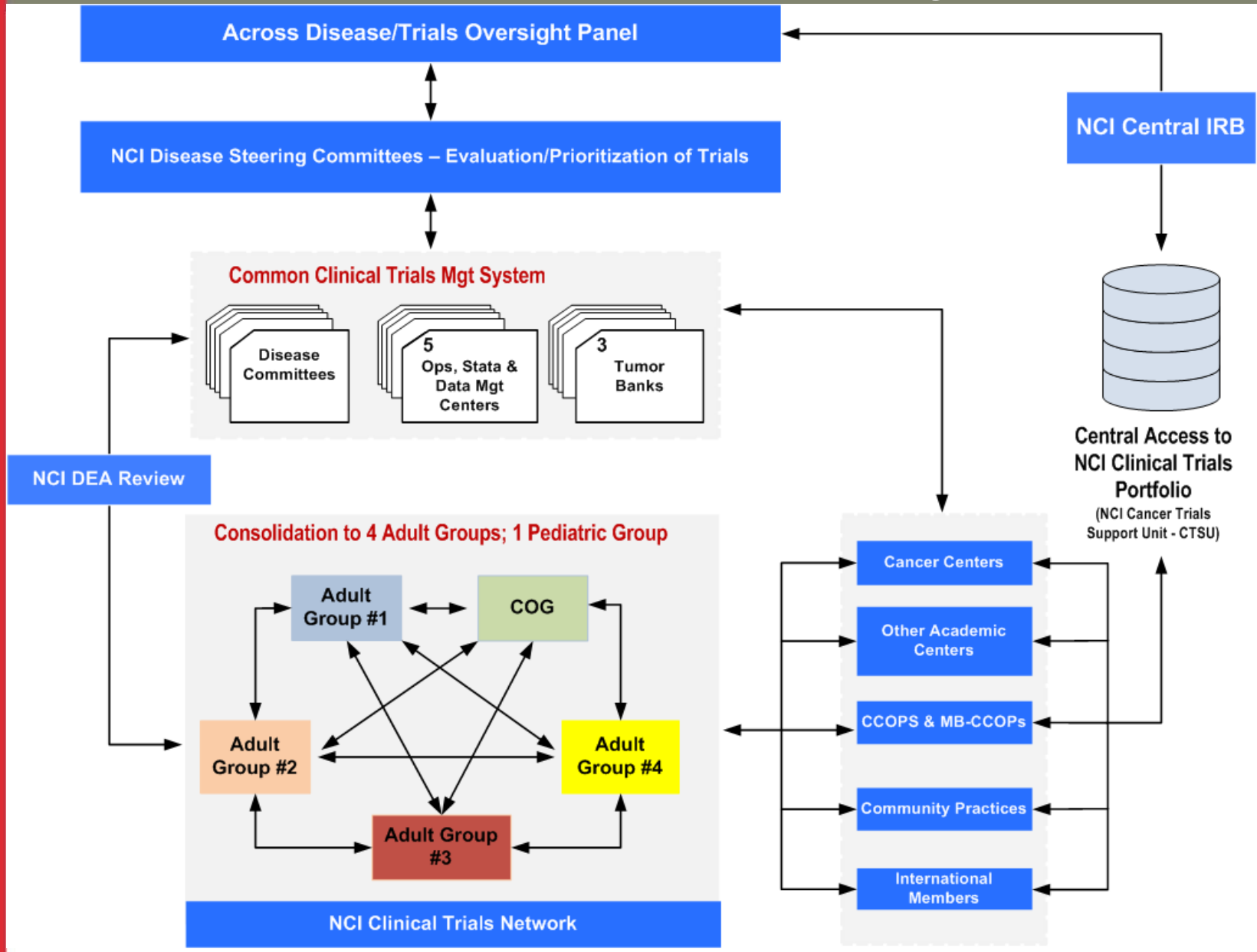
Proposed New Organizational Structure for the NCI's Clinical Trials Program



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How to Implement Change?

New NIH grant application guidelines require a new Funding Opportunity Announcement (FOA) for the Group Program

- Stop accepting renewal applications for 2011; continue funding via supplements until new FOA available
- Develop a completely new FOA for a National Clinical Trials Network that envisions all of the changes outlined and which would welcome proposals from current grantees and Cancer Centers or others
- Propose a specific date for receipt of new applications based on new guidelines when everyone will have to compete (in a single coordinated review) to be part of the new system

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Tentative Timeline for Change

Timeline for Development of New FOA & Guidelines for System and for Submission, Review, and Support of new Awards

Dec 2010 – Jul 2011:	Gather information/input from stakeholders & community for New FOA & Guidelines; develop Concept
Aug 2011:	NCI Divisional/CTROC Concept Review
Sept 2011:	NCI Scientific Program Leadership Concept Review
Nov 2011:	BSA Concept Review
Nov 2011 – Mar 2012:	NCI DEA Review of FOA & Guidelines
Mar 2012 – July 2012:	NIH Review of New FOA & Guidelines
July 2012	New FOA Released/Published
Nov 2012	Receipt of Competing Applications for New FOA
Feb 2013	Review of Competing Applications by DEA
May 2013	NCAB Review
After Oct 2013	Rollout of Awards in FY2014

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Developing A National Clinical Trials Network: Next Steps

- Work with Groups and critical stakeholders: Current Cooperative Group PIs, CCOP PIs, ASCO, AACR, 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 and advocates
- 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
- Simultaneously advance ongoing work on other issues raised by IOM: tissue banks, funding, efficiency, coordination, correlative science, etc.