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Request for Application (RFA)

U10 Cooperative Agreement for NCI Clinical Trials Network

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on behalf of the

Division of Cancer Treatment & Diagnosis:
Biometric Research Branch, Cancer Diagnosis Program, Cancer Imaging Program, Cancer Therapy Evaluation Program, and Radiation Research Program

Division of Cancer Prevention:
Community Clinical Oncology Program (CCOP) & Minority-Based CCOP

Presentation to BSA
November 7, 2011

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Revamping the Clinical Trials Systems at NCI

Improve speed & efficiency of development & conduct of trials

- ✓Cancer Trials Support Unit - provide 24/7central registration & collection regulatory documents
- ✓Provide NCI Central IRBs – Adult and Pediatric
- ✓Qualify sites for advanced imaging

Incorporate innovative science and trial design

- ✓NExT – multiple agents under development, with external peer review
- ✓Clinical Assay Development Program (CADP)
- ✓Develop support & funding for non-Group investigators with novel ideas

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Why Support a Standing, Publicly Funded Clinical Trials Network?

- Advance science & patient care, especially on important research questions that are not priorities for industry, including evaluating:
  - Integration of new agents into standard regimens
  - Combinations of novel agents developed by different sponsors
  - Multi-modality regimens (e.g., Surgery, Radiotherapy, IP therapy)
  - Therapies for pediatric cancers, rare cancers, and uncommon presentations of more common cancers
  - Screening, diagnostic, & prevention strategies
  - Optimal duration and dose of drugs & radiotherapy
  - Different treatment approaches already approved for clinical care

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Why Support a Standing, Publicly Funded Clinical Trials Network?

- Trials oriented toward disease-management, not agent-specific or limited by marketing constraints, with inclusion of research questions related to:
  - Correlative science
  - Imaging
  - Quality of Life
  - Symptom Management
  - Special Populations (e.g., analyis by sex, age, race/ethnicity)
- Extensive, direct involvement of entire oncology community in the design, development, & conduct of trials:
  - Academic center investigators
  - Community & private practice investigators
  - Patient advocates
  - Young investigators in training
  - International collaborators
  - Data-sharing of clinical data & banked biospecimens

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Selected Major Accomplishments of Program: 2005 - 2011

- Over 30 Practice-Changing Clinical Trials including therapeutic agents and other modalities, with 4 announced in first 6 months of 2011
  - ACOSOG-Z0011 – Surgery: SLND not inferior to Axillary Dissection in SLN+ BC
  - NCIC-CTG MA.20 – RT: Regional Nodal RT reduces LR & improves DFS in Node+ BC
  - COG-AALL0232 – Pediatrics: High Dose MTX improves EFS in pediatric ALL
  - RTOG-94-08 – Multimodality: Short-term ADT with RT improves OS in prostate cancer
- Over 10 FDA Indications - New Oncology Agents (Yr FDA Approval)
  - Bevacizumab – CRC (2006); NSCLC (2006); Renal Cell Cancer (2009)
  - Imatinib mesylate – Pediatric CML (2006); Adjuvant GIST (2008)
  - Nelarabine – T-ALL and T-LBL (2005)
  - Rituximab – Diffuse Large B-cell Lymphoma (2006); Follicular NHL (2006)
  - Trastuzumab - Adjuvant Therapy for Early-stage Her2+ Breast Cancer (2006)
  - Thalidomide – Newly Diagnosed Multiple Myeloma (2006)
  - Anti-GD2 Antibody (ch14.18) in Neuroblastoma (BLA Currently in Preparation)
- Examples: New Indications Generic Agents (Yr Publication/Press Release)
  - Daunorubicin in AML (2009); Dexamethasone in Multiple Myeloma (2007)

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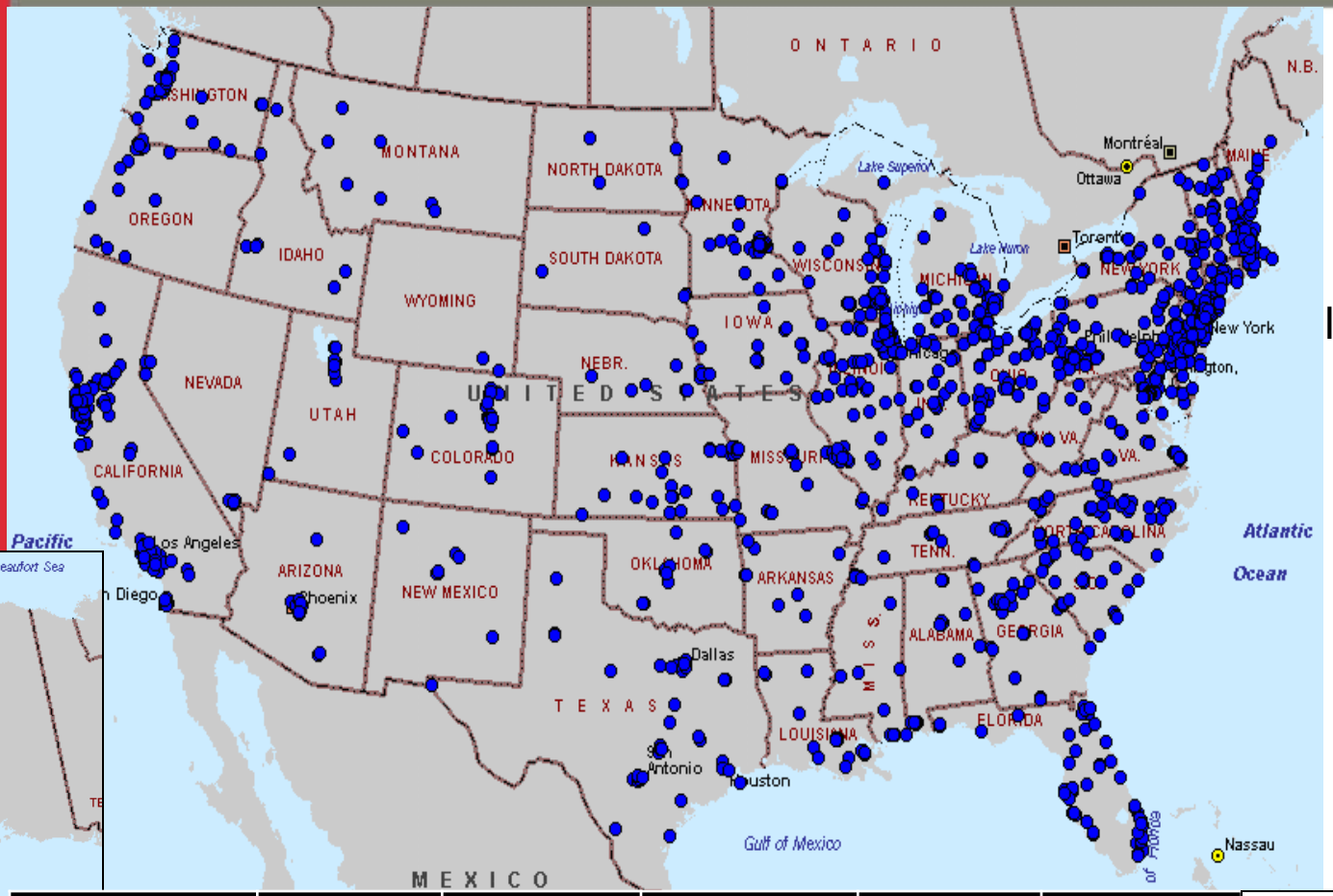
Overview of the Program



3,100 Institutions

14,000 Investigators

About 25,000 pts enrolled on tx trials annually

Trials	FY2006	FY2007	FY2008	FY2009	FY2010
All Phases: Treatment Trials	27,667	24,715	25,784	29,285	23,468

Accrual Distribution:

Phase 3: 83.4%

Phase 2: 15.1%

Phase 1/Pilot: 1.5%

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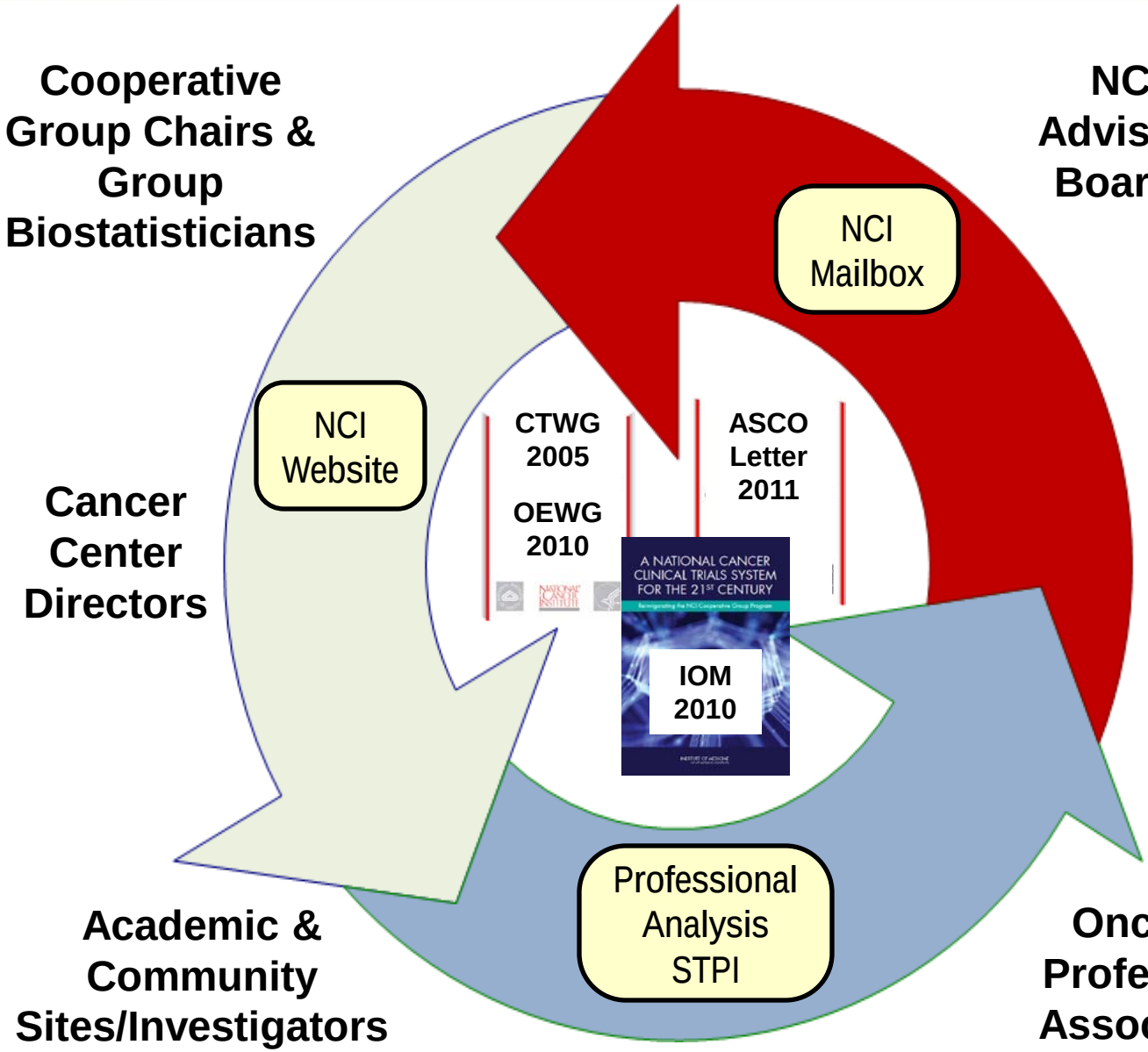
Extensive Review & Stakeholder Input Revised NCI's Clinical Trials System



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Progress Toward Consensus Goals for a Transformed System

Improve speed & efficiency of development & conduct of trials

- ✓ Implementation of operational efficiency timelines
- ✓ Implementation of Common Data Mgt System for all trials

Incorporate innovative science and trial design

- ✓ Implementation of BIQSFP program for integral & integrated biomarkers, imaging, and quality of life studies in trials
- ✓ Encourage randomized phase 2 trials

Improve trial prioritization, selection, support, & completion

- ✓ Disease-specific and specialty Steering Committees prioritize trials
- ✓ Implementation of slow accrual guidelines

Ensure participation of patients & physicians in system

- ✓ Pilot initiatives for increased reimbursement for phase 2 and 3 trials
- ✓ Pilot initiatives to assess physician & patient feedback on trials to enhance accrual

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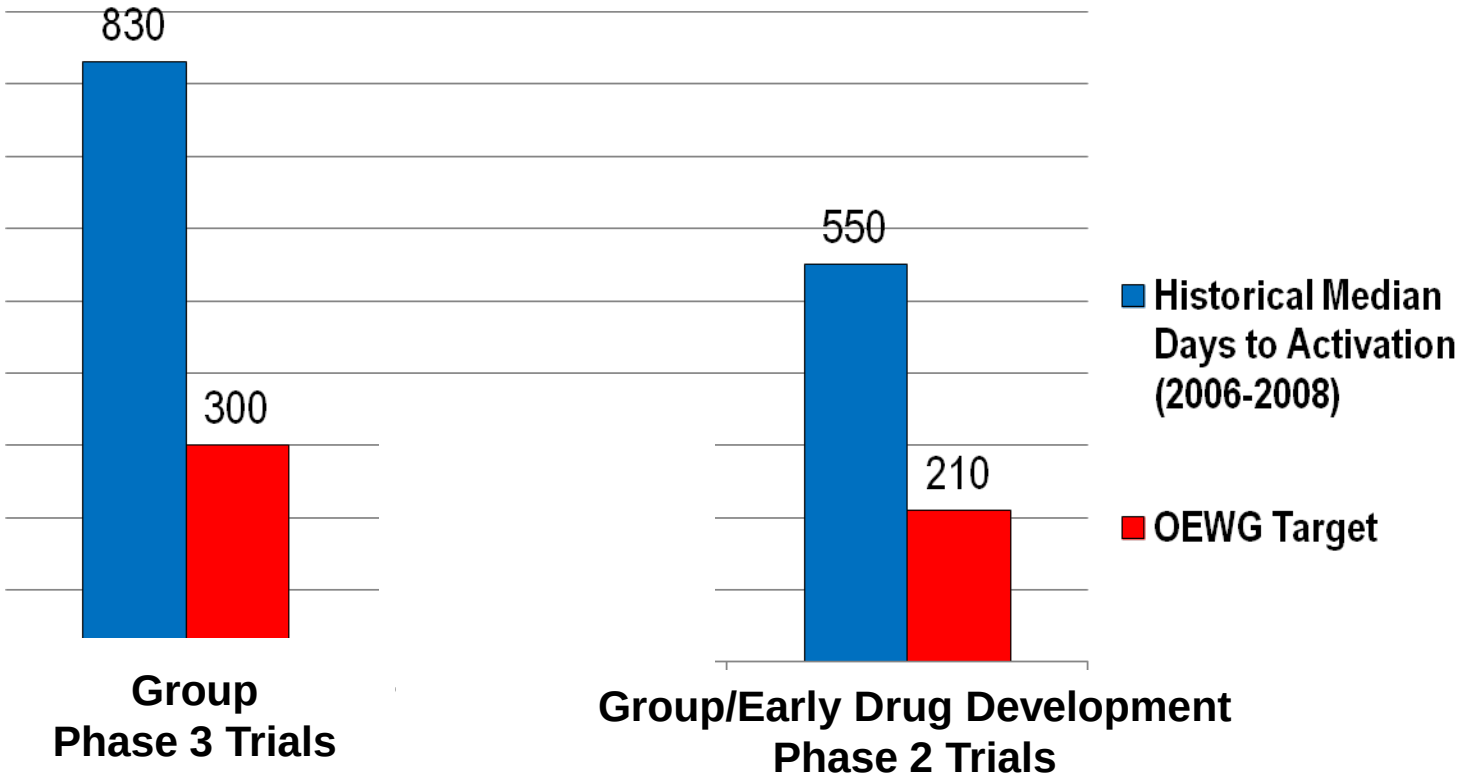
Operational Efficiency: Aggressive But Necessary New Targets



Timelines include IRB approval, industry negotiations, & FDA approval

Phase 3 trial development stopped if not open in 2 years
Phase 2 trial development stopped if not open in 18 months

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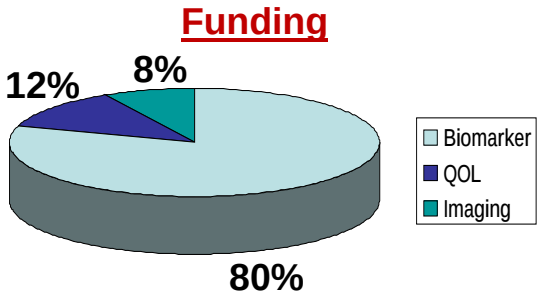
Incorporating Innovative Science and Trial Design Into Late Phase Cancer Clinical Trials

Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) ensures critical correlative science incorporated into phase 3 and large phase 2 trials

From 2008-2011, 13 phase 3 trials received support totaling over $22 Million

Phase 3 Trial Examples:

- COG: AAML0531: Evaluation of Bortezomib and Sorafenib for patients with de novo AML & FLT3 ITD (high allelic ratio)



- RTOG-1010: Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma

- S1007: Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone-responsive and HER2-negative Breast Cancer According to Gene Profile/Recurrence Score

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Disease-Specific Steering Committees : Prioritizing Clinical Trials

Steering Committee	Year Established	Co-Chairs as of 10-7-2011 Disease-Specific Steering Committees (SCs)
GI	2006	Dan Haller, MD & Joel Tepper, MD (Incoming Co-Chair Neal Meropol, 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 & Robert Arceci, MD, PhD (Hematology) Mark Bernstein, MD & Katherine Matthay, MD (Solid Tumors)

***Cancer Center Directors**

Over 170 Concepts evaluated since inception of SCs

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Related Steering Committees as of 10-7-2011: (Non-disease Focus)

- Investigational Drug Steering Committee
  - Co-Chairs: Pat LoRusso, DO, & Dan Sullivan, MD
- Clinical Imaging Steering Committee
  - Co-Chairs: Steven Larson, MD & 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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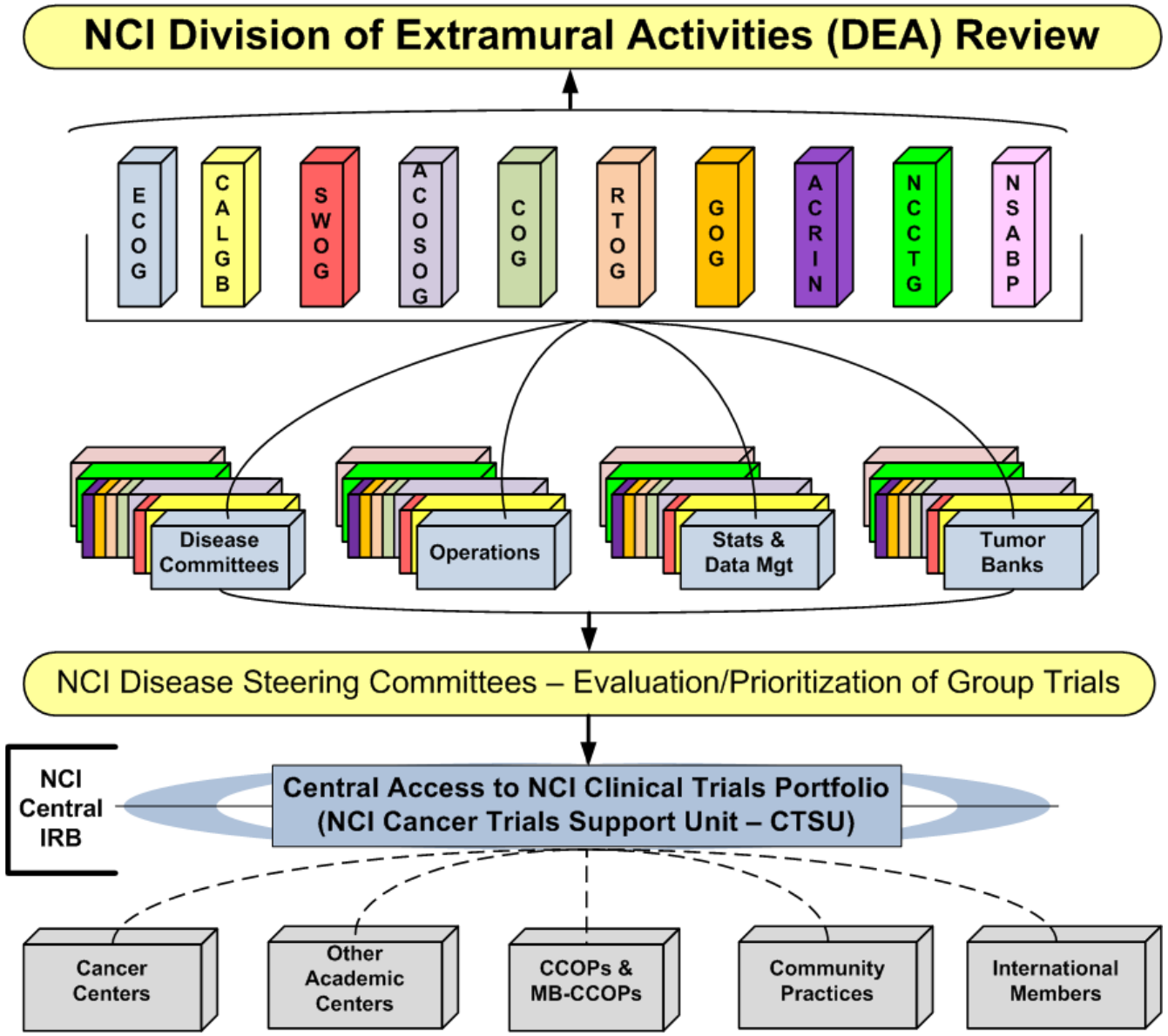
Structure of Program: As of January 2011



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Next Steps in Transforming the System

- New RFA for an Integrated National Clinical Trials Network
- Consolidated Organizational Structure with Funding for 1 Pediatric Group and up to 4 Adult Groups
- Review Criteria with Emphasis on Integration & Collaboration for Overall Scientific Achievement and Operational Efficiency
- Funding Model with Increased Per-Case Reimbursement for "High-Performance" Academic & Community Sites
- Competitive Integrated Translational Science Awards
- Revitalize Cancer Center Role in the Network (U10 awards)

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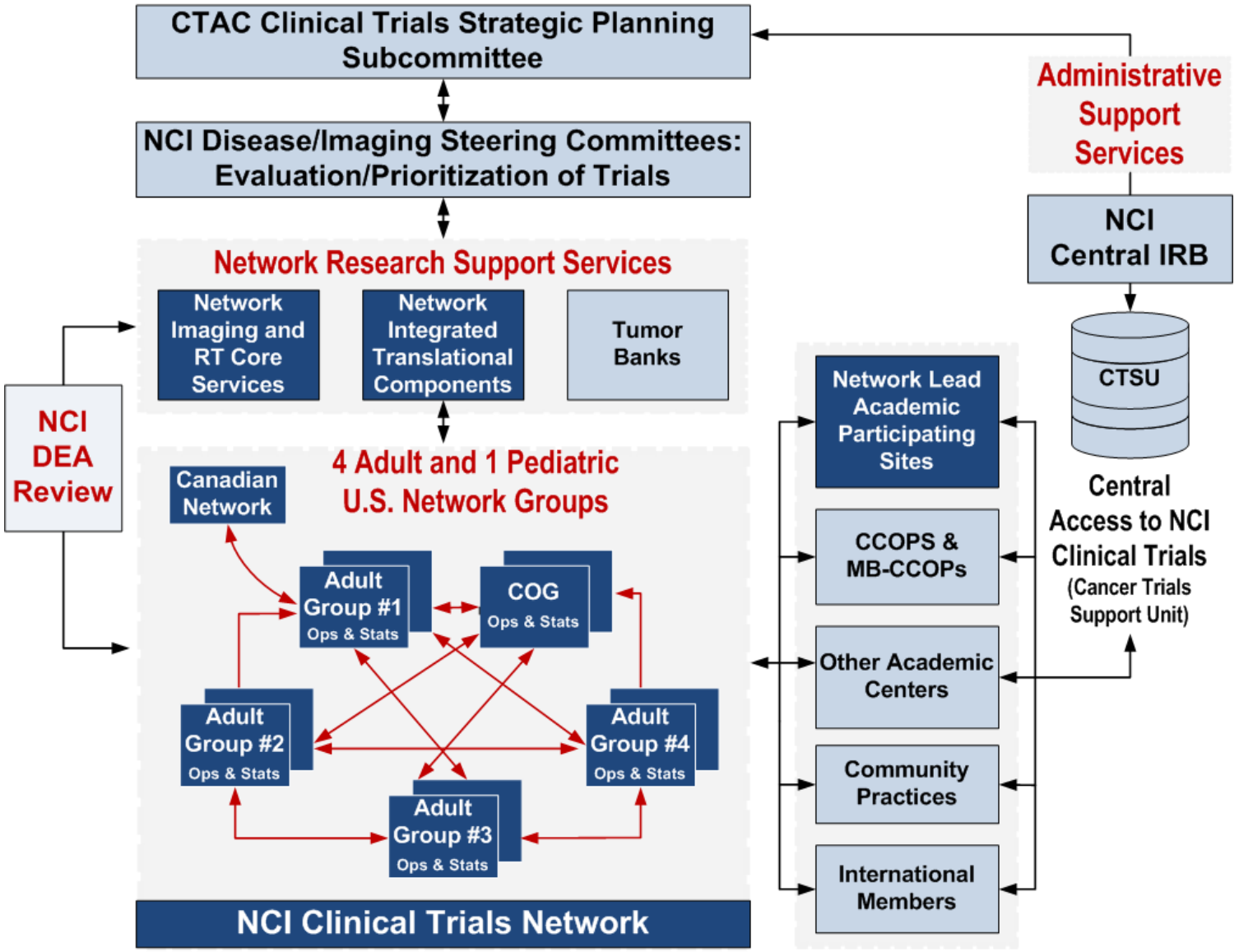
Introducing A New Organizational Structure
NCI Clinical Trials Network



Dark blue boxes signify NCI DEA reviewed, grant-funded components under this RFA

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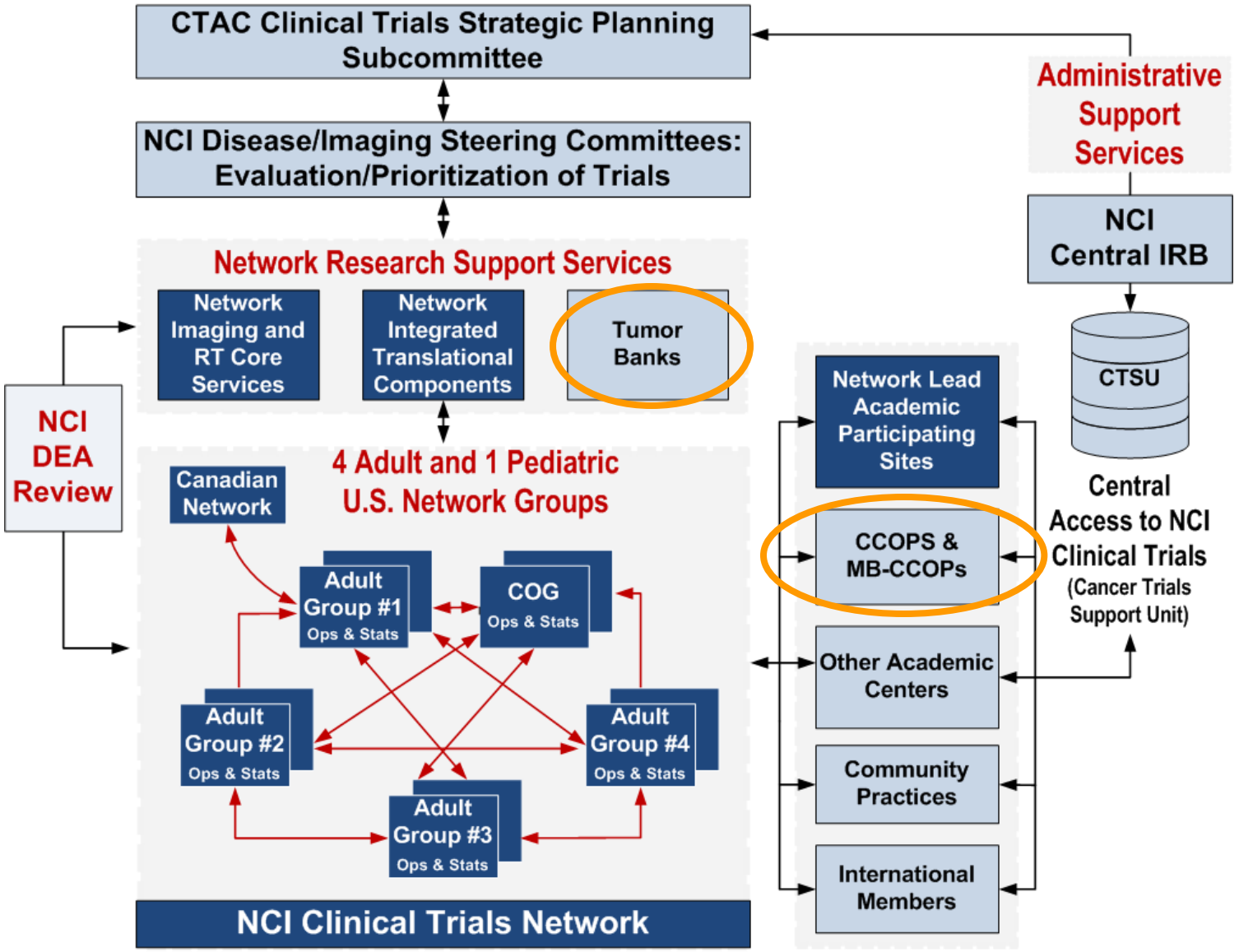
Introducing A New Organizational Structure
NCI Clinical Trials Network



Other NCI Grant Programs

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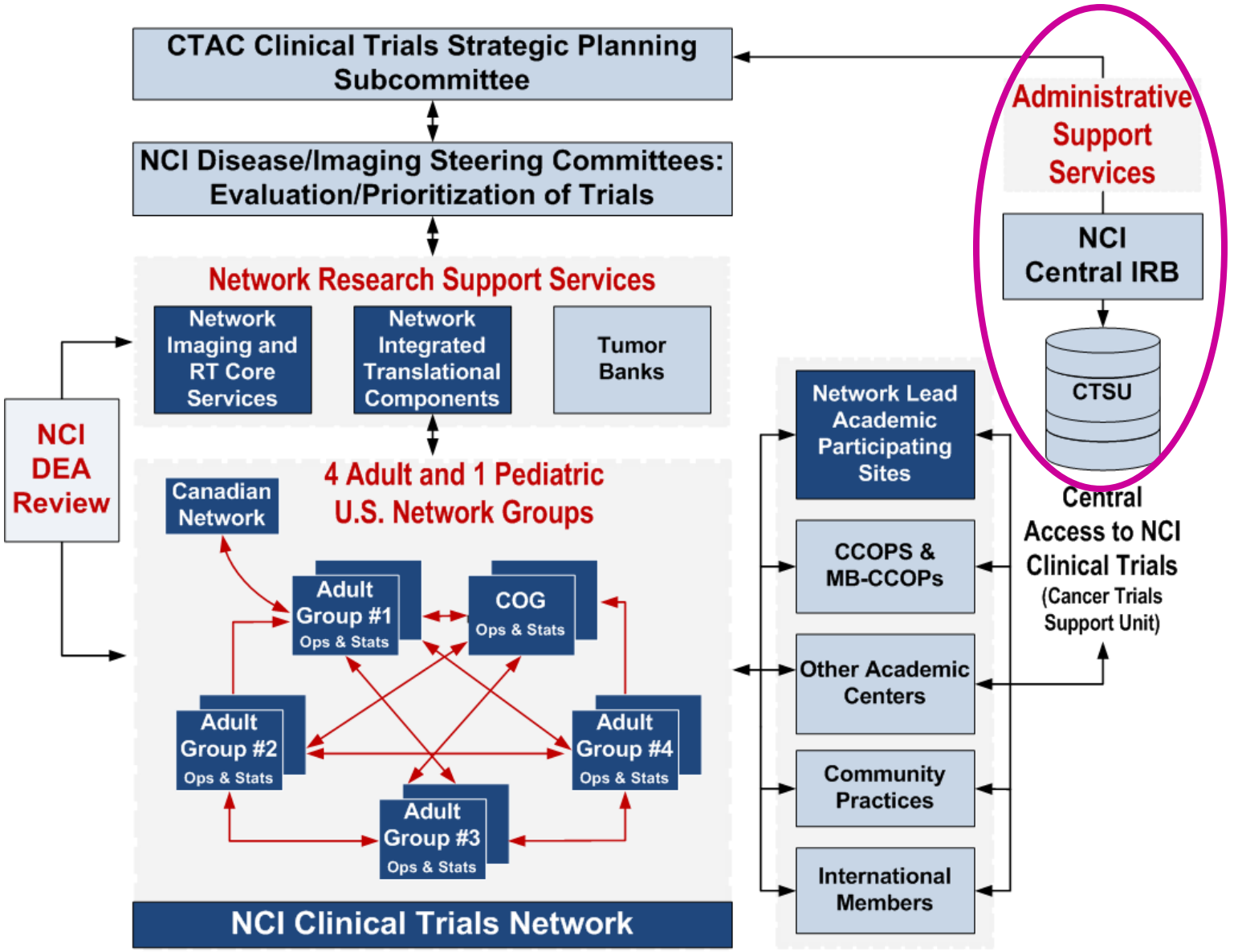
Introducing A New Organizational Structure
NCI Clinical Trials Network



Contract Programs

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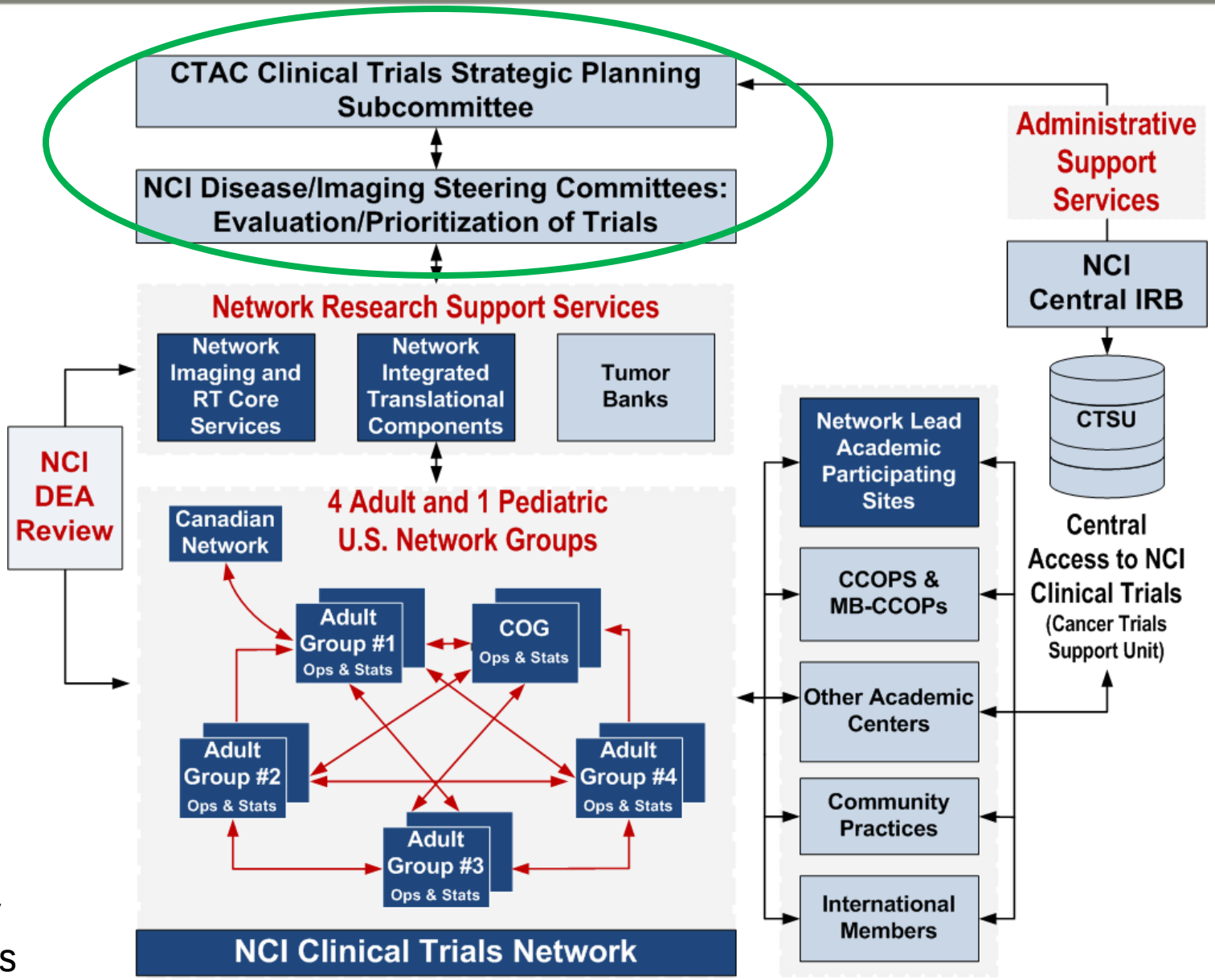
Introducing A New Organizational Structure
NCI Clinical Trials Network



Extramural & Advisory Committees

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Rationale for Transforming Current Program:
How Will Consolidated Network System Help?

- Consolidate infrastructure to gain efficiencies (e.g., IT, Regulatory, Administrative, Tissue Resource Management)
- Consolidate Imaging & RT core services to benefit entire Network
- Integrate new components into trials to provide value-added research questions (e.g., advanced imaging, translational science)
- Integrate new agents into trials
  - Ex: Erlotinib, crizotinib, & ipilimumab are being integrated into trials in earlier stages of lung cancer & melanoma treatment requiring screening large populations & combining the agents optimally with surgery, RT, and immunotherapy
- Evaluate new agents in molecularly-defined disease subsets
  - Ex: Even for common diseases such as breast cancer, # of molecularly-defined patient subsets is increasing & there is a need for trial prioritization evaluating multiple new agents with standard regimens across subsets to avoid duplication & optimize accrual

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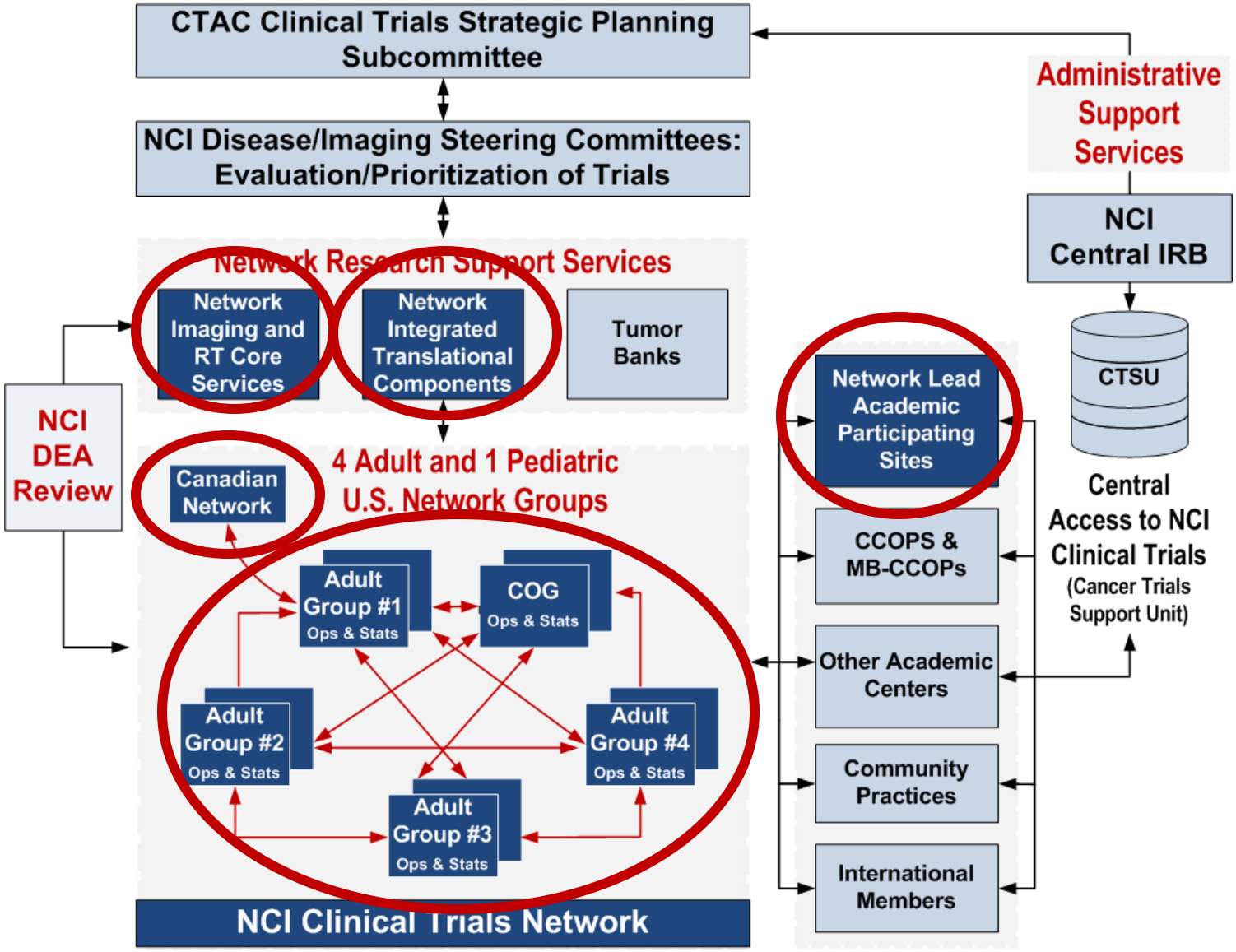
Introducing A New Organizational Structure

NCI Clinical Trials Network



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Network Component Description
Group Operations Ctrs & Group Stats Ctrs

- Provide scientific strategy & goals across broad range of diseases
- Responsible for Network Group administration including
  - Study conception, protocol development, and accrual to trials
  - Adherence to "Operational Efficiency" timelines
  - Audits and QA/QC of protocol therapy
  - Coordinating biospecimen collection from patients on trials
  - Compliance with FDA, OHRP, NCI/NIH regulations
- Statistical leadership for effective design & trial conduct
- Monitors data quality for primary analysis & correlative science
- Supports data mgt & analyses for studies outside the Network Groups as appropriate (e.g., Steering Committee-approved studies)

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Network Components Review Criteria
Group Operations & Statistical Centers

- Reconfigure NCI/NIH external peer-review of System
  - Emphasis on incentives for a national system with trials open to all qualified sites & sites able to credit any Group to which they belong
  - Review of all Network Groups/components at same time (specific review panels for particular Network components)
  - Scientific evaluation will shift to evaluating Group role in national network, overall scientific strategy, innovation and quality (~50%)
  - Review criteria for operational efficiency & collaborative management of Network (~50%)
    - ✓ Coordination with other Network Groups, NCI programs, NCI investigators outside Groups (e.g., CCOPs, MB-CCOPs, Tumor Banks, Cancer Centers, SPORES, N01s/U01s, P01s, etc.)

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Network Description & Review Criteria
Lead Academic Participating Sites

- Description
  - Multiple-PI grants for academic institutions with demonstrated scientific leadership in **≥ 1 adult Network Groups, substantial** accrual, & excellent data quality ("high-performance" sites)
  - Targeted at NCI Comprehensive and Clinical Cancer Centers and other leading academic centers

- Review Criteria
  - Meets accrual threshold set from trials across entire Network
  - Expertise & leadership role in Group(s)
  - Data quality
  - Contributions to translational science within Group trials
  - Scientific collaborations across Cancer Center/Institution & Network

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Network Description & Review Criteria
Integrated Translational Science Awards

- **Description**
  - Multiple-PI grants to support prominent researchers for their expertise and efforts in incorporating molecular studies into Network trials & enabling acquisition of preliminary data for further research
  - Laboratory-based researchers will also facilitate hand-off of early phase clinical trial findings into later phase, definitive trials

- **Review Criteria**
  - Peer-review of quality of scientific approach & plans for integration of translational science into clinical trials
  - Leverages independently funded laboratory resources with Group clinical specimens & data to benefit Group research aims
  - Research area likely to benefit trial efforts across Network

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Network Description & Review Criteria
Core Services & Canadian Partner Network

- RT and Imaging Core Services
  - Provides scientific leadership for incorporating appropriate QA & image data management for research trials involving RT & imaging
  - Review Criteria for scientific leadership & expertise as Network-wide resource, integrated IT platforms for capturing and storing images, & efficient procedures for accessing site data for RT & image-related trial questions
- Canadian Collaborating Trials Network
  - NCI Program has had long history of collaboration with Canadian sites and non-profit Canadian clinical trial organizations
  - Review Criteria for ability to provide appropriate regulatory oversight for US Networks trials conducted in Canada, irrespective of which Group leads trial and to be full partners in accruing patients to US Network trials

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Overview of RFA: Cooperative Agreement FOAs and Estimated # Grants

Network Component	Mechanism (Duration)	Est. Max. # Grants	Frequency New Application Accepted?	Multiple PI Option?
Group Operations Centers	U10 (5 Yrs)	5	Every 5 Years	Yes
Group Statistical & Data Mgt Centers	U10 (5 Yrs)	5	Every 5 Years	Yes
Canadian Collaborating Network	U10 (5 Yrs)	1	Every 5 Years	Yes
Integrated Translational Science Awards	U10 (5 Yrs)	1 to 5	Every 5 Years	Yes
RT and Imaging Core Services	U24 (5 Yrs)	1 to 2	Every 5 Years	Yes
Lead Academic Participating Sites	U10 (5 Yrs)	30 to 40	Any Year	Yes

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Principles of Network Funding Plan

- All external reviews of the NCI clinical trials system emphasized need to provide increased research reimbursement to ensure continued participation of sites in the public program

- Base "per-case" reimbursement for patient enrollment in the program has remained fixed at $2,000 per patient in treatment trials for over a decade
  - 2006 estimate for average per patient cost in industry trials was $4,700 for phase 3 & $8,450 for phase 2 Trials (& some industry trials at **≥ $15,000)**
  - Survey in 2009 of Group sites found that of those planning to limit participation in the program (32% of respondents), 75% cited inadequate reimbursement for the decline in their level of participation

- "High-Performance" sites incur additional infrastructure costs due to the number of patients they accrue & additional funding is especially needed to compensate these sites for their large patient follow-up burden - (propose additional $2,000 /pt for these sites for total of ~$4,000/pt)

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Budget History for Components of NCI National Clinical Trials Network

Base Divisional Set-Aside for Network/Group Program *	FY2006	FY2007	FY2008	FY2009	FY2010	FY2011 (Estimated)	Grand Total (Over 6 Yrs)	% Grand Total
Group Operations & Statistical Centers (including Capitation for Majority of Accrual)	$128,833,204	$126,516,480	$126,141,046	$126,380,185	$127,127,666	$120,304,563	$755,303,144	78.7%
Participating Site U10s	$ 12,532,773	$11,375,647	$11,074,808	$11,241,179	$11,823,333	$10,839,407	$ 68,887,147	7.2%
Core Services for Imaging & RT (RPC, QARC)	$ 4,185,608	$4,302,227	$ 4,271,987	$ 4,224,437	$ 4,307,091	$ 4,131,527	$25,422,877	2.6%
Subtotal	$145,551,585	$142,194,354	$141,487,841	$141,845,801	$143,258,090	$135,275,496 **	$849,613,167	
Estimated CTSU Capitation	$ 4,000,000	$ 3,779,781	$ 4,289,927	$ 5,162,362	$ 5,174,165	$ 5,040,000	$ 27,446,235	2.9%
Subtotal	$ 149,551,585	$145,974,135	$145,777,768	$147,008,163	$148,432,255	$140,315,496	$877,059,402	
ACRIN	$7,002,444	$15,442,054	$13,129,762	$13,509,478	$12,816,778	$10,612,813	$ 72,513,329	7.6%
ATC	$1,644,551	$ 1,749,999	$ 1,716,026	$ 1,716,026	$1,716,030	$ 1,716,026	$ 10,258,658	1.1%
Grand Total	$158,198,580	$163,166,188	$160,623,556	$162,233,667	$162,965,063	$152,644,335	$959,831,389	100.0%

*** Does not include ARRA funding and special "one-time" supplements (e.g., transition supplements) or funding provided by other NCI/NIH Programs for Special Initiatives (e.g., complexity funding)**

**** Base funding was decreased by FY2011 general budget cuts**

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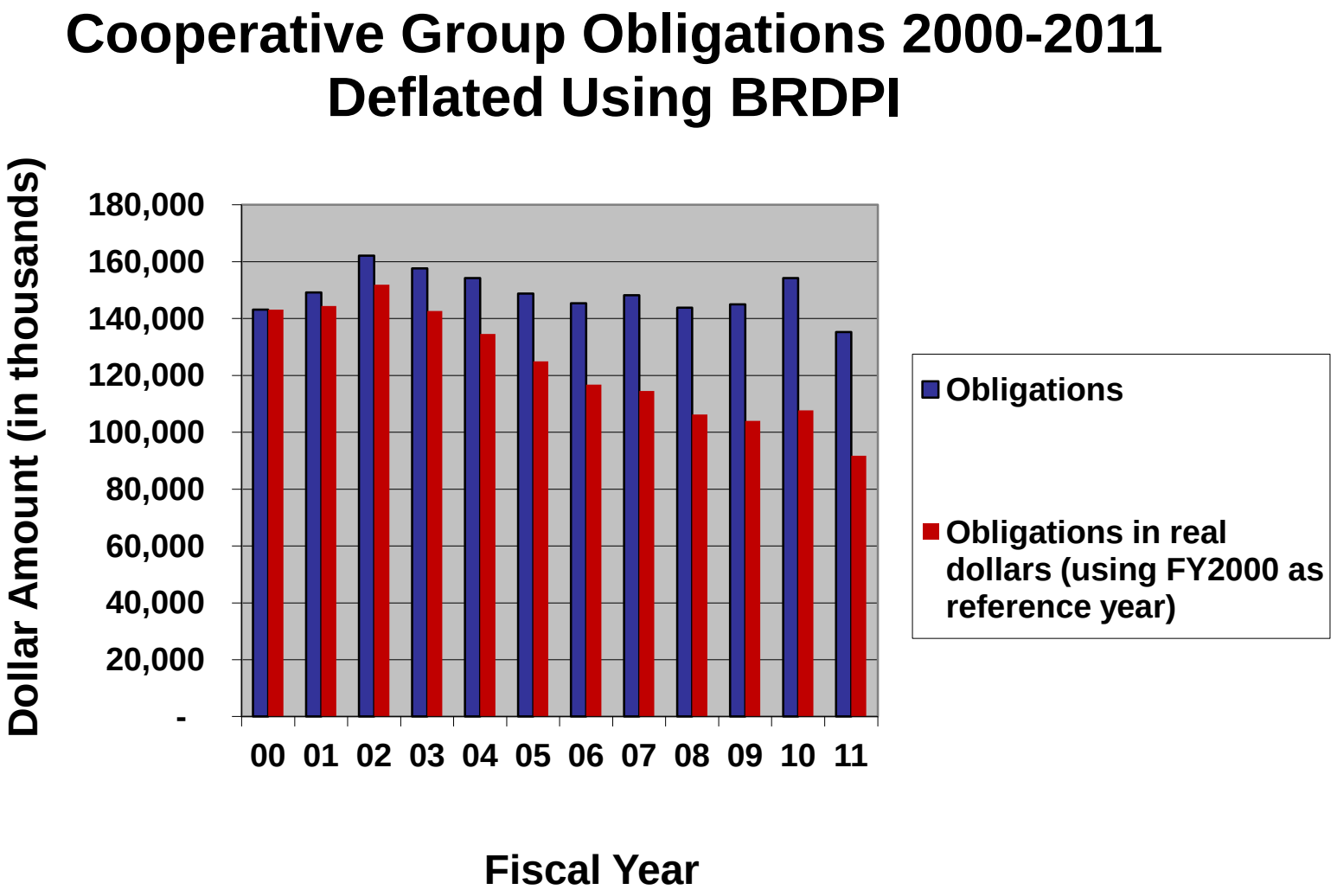
Trials Program Funding 2000 to 2011: Real $



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5-Year Annual Funding Request for NCI Clinical Trials Network

Category for Base Division Set-Aside for Network Program	Annual Total Cost for FY14 to FY18 Based on 20% Reduction in Accrual Compared to Average Accrual Over Last 6 Years (Approx. 20,000 Treatment Trial Enrollments)
Funding Based on FY2011 Levels:	
Group Operations & Statistical Centers (includes Capitation), Lead Academic Participating Sites, and Core Services	$ 152,644,335
Funding Request Based on New Funding Model & BIQSFP:	
Increase Capitation to "High-Performance" DCTD-funded Sites	$ 11,520,000
Increase Capitation to "High-Performance" DCP-funded CCOPs & MB-CCOPs	$ 10,080,000
Increase Funding for Integral and Integrated Markers (BIQSPF)	$ 4,000,000
Subtotal:	$ 25,600,000
Grand Total:	$ 178,244,335 *

*** The 5-Year Total Cost Funding Request for FY2014 to FY2018 for the NCTN is $891,221,675**

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Strategic Planning for the New NCTN Program

- Treatment trial accrual has been dominated by Breast and GI Cancer trials, especially large adjuvant trials, over past decade
- The new funding model will require Network organizations and Steering Committees to monitor the balance of trials prioritized for development and help develop a strategic consensus about the diseases in which to encourage more trials as scientific opportunities arise
- New review criteria should facilitate more trials in disease areas which have been typically underrepresented, relative to their incidence, and portfolio balance will be monitored closely by CTAC's NCTN Strategic Planning Subcommittee to ensure that scientific opportunities in less common tumors are not missed

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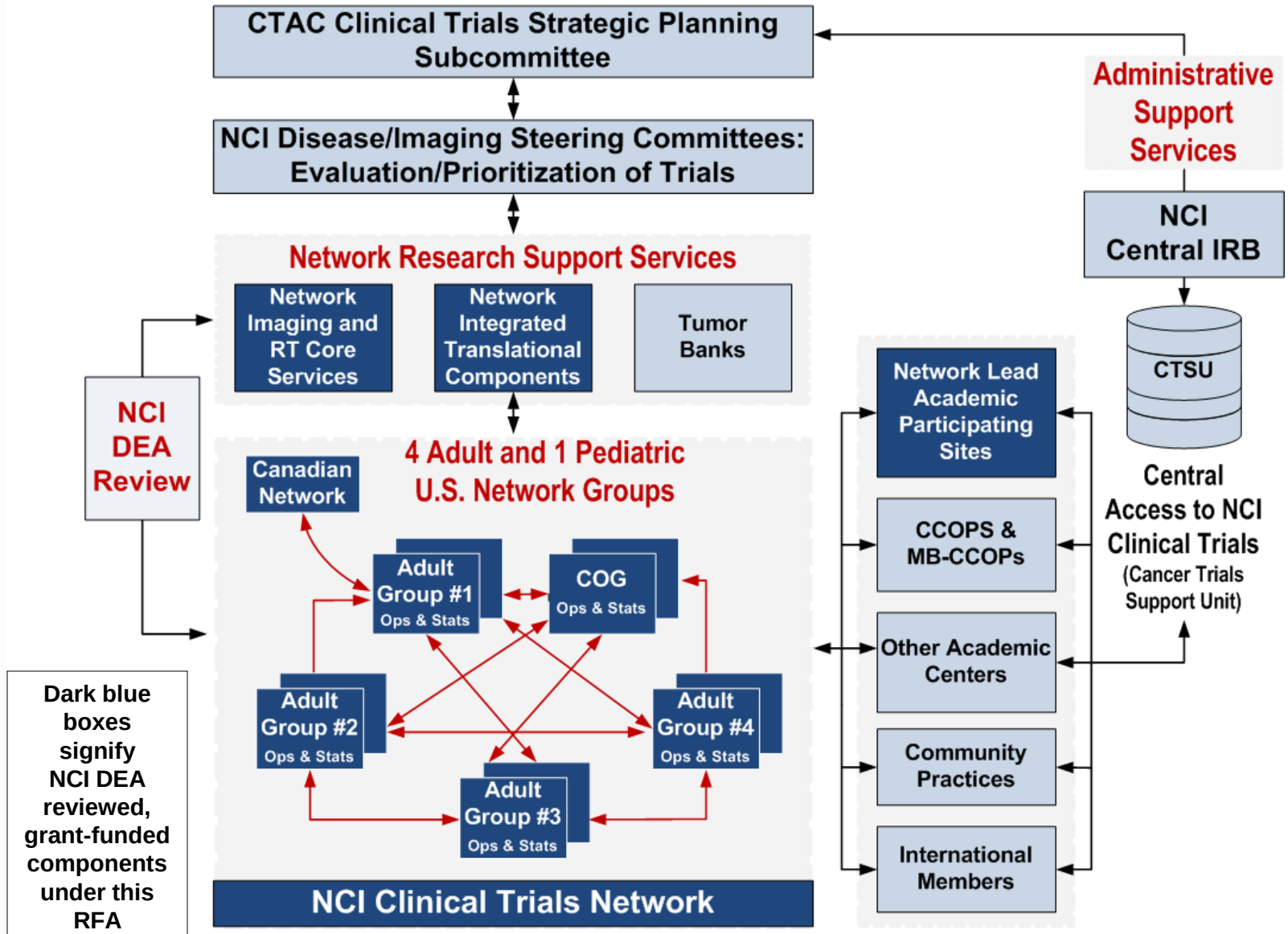
Introducing A New Organizational Structure
NCI Clinical Trials Network



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