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Restructuring the National Cancer Clinical Trials and Translational Research Enterprise

Update for the NCAB

James H. Doroshow, MD

February 3, 2009

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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CTWG Restructuring Initiatives

- Enterprise-Wide/Integrated Management

  Restructure the extramural and intramural oversight of NCI clinical trials

- Prioritization/Scientific Quality
- Coordination
- Standardization
- Operational Efficiency

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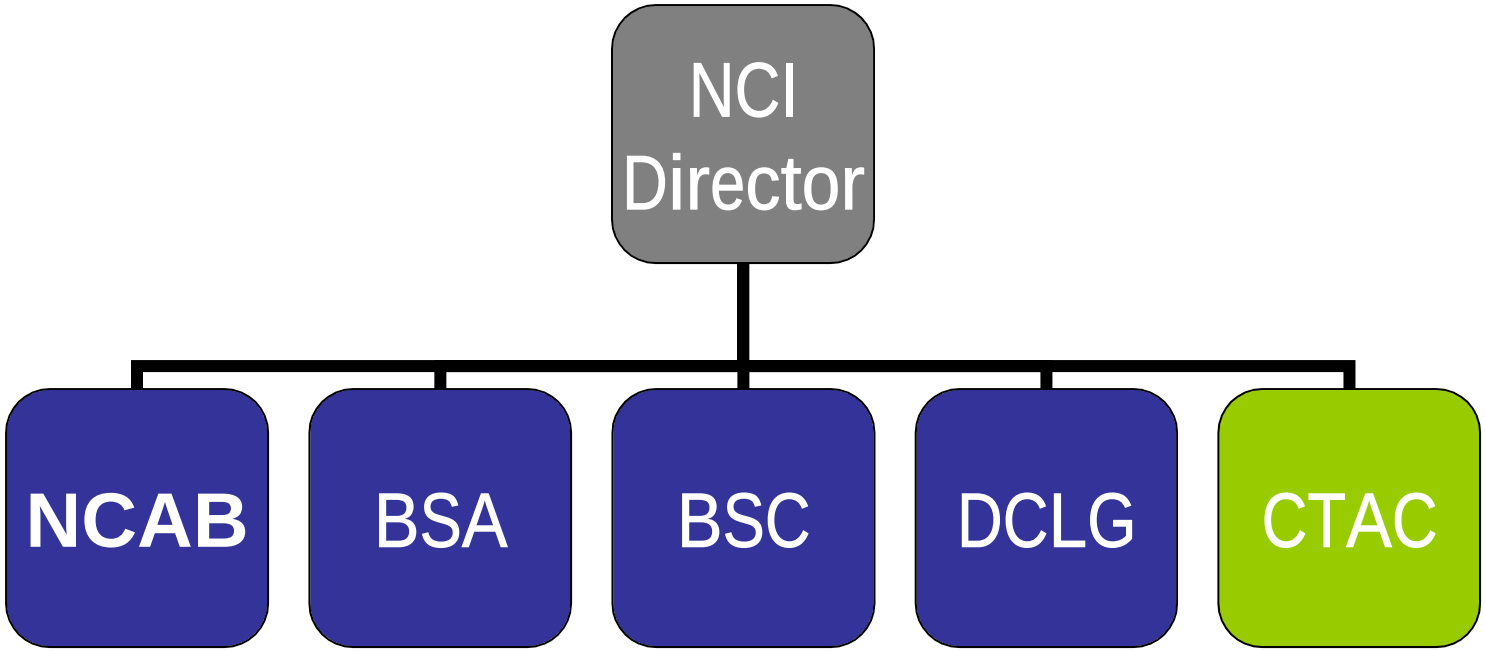
NCI Federal Advisory Groups



http://deainfo.nci.nih.gov/advisory/ctac/ctac.htm

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Clinical Trials & Translational Research Advisory Committee (CTAC)

- Oversight of CTWG Implementation
  - Steering Committee Activities
  - Correlative Science Working Group: Prioritization & Standards
  - Standardization Projects: Clinical Trials Database; Clinical Trials Management System Working Group
  - CIRB utilization
- Coordination Subcommittee
- CMS and FDA interactions with NCI
- Cooperative Group Complexity Model for Funding
- TRWG Implementation

  7th meeting, March 4, 2009; http://deainfo.nci.nih.gov

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CTWG Restructuring Initiatives

- Enterprise-Wide/Integrated Management
- Prioritization/Scientific Quality

  Involve all stakeholders in design and prioritization of clinical trials that address the most important questions, using the tools of modern cancer biology

- Coordination
- Standardization
- Operational Efficiency

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Prioritization: Scientific Steering Committees

- Investigational Drug Steering Committee (IDSC) for early phase trial prioritization

- Disease-Specific Scientific Steering Committees (SC's) for phase 3 trials and selected phase 2 studies

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Investigational Drug Steering Committee

- Provide strategic input into the clinical development plans for new agents for which CTEP holds the IND
- Co-Chairs: Michael Grever, MD and Charles Erlichman, MD
- Membership includes PI's of NCI's early phase U01 grants and N01 contracts and representatives from Cooperative Groups and other content experts
- Task Forces (9):
  - Signal Transduction; Biomarker; Angiogenesis; Clinical Trial Design; Pharmacology; Immunotherapy; PI3K/Akt/mTOR (PAM); Cancer Stem Cells; DNA Repair and Programmed Cell Death

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IDSC Accomplishments

- Transparency and enhanced scientific input into NCI drug development process
  - IGF-1R inhibitor (9/06)
  - cdk inhibitor (6/08)
  - hedgehog inhibitor (11/08)
  - gamma secretase inhibitor (1/09)
- Identify niches for NCI involvement unattractive to industry
- Developed recommendations for:
  - Toxicity management of anti-angiogenic agents
  - Novel Phase 1 and Phase 2 clinical trial designs
  - Prioritization of agents for immunotherapy trials
  - Guidelines for incorporation of biomarkers into early phase trials
- Transition from IDSC to Phase 3 Steering Committees facilitated by designated liaisons

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Disease-Specific Steering Committees: Responsibilities

- Prioritize phase 3 and selected phase 2 concepts for therapeutic clinical trials
- Refine & collaborate on phase 3 and selected phase 2 concepts utilizing Task Forces when appropriate
- Convene Clinical Trials Planning meetings to identify critical issues/questions for study in the disease
- Information exchange on phase 2 and other studies
- Periodically review accrual and unforeseen implementation issues

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Disease-Specific Steering Committee

Committee Composition:

Major Components of Oncology Community Represented

- Cooperative Groups
- SPORES / Cancer Centers, R01 / P01 investigators
- Community Oncologists
- Biostatisticians
- Patient Advocates
- IDSC and Sx Mgt / HR-QOL SC representatives
- NCI staff
- Plus Invited Observers:
  NCI Leadership, Cooperative Group Chairs

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Initial Steering Committees

- Gastrointestinal Cancer (Co-Chairs: Joel Tepper, MD & Daniel Haller, MD)
- Gynecologic Cancer (Co-Chairs: William Hoskins, MD & Gillian Thomas, MD)
- Head and Neck Cancer (Co-Chairs: Arlene Forastiere, MD, David Schuller, MD, & Andrew Trotti, MD)
- Symptom Management and Health-Related Quality of Life (Co-Chairs: Deborah Bruner, RN, PhD & Michael Fisch, MD, MPH)

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New Steering Committees

- Genitourinary Cancer (Co-Chairs: Anthony Zietman, MD, George Wilding, MD, & Eric Klein, MD)
- Breast Cancer (Co-Chairs: Charles Geyer, MD & William Wood, MD)
- Thoracic Malignancy Steering Committee (David Harpole, MD, William Sause, MD, & Mark Socinski, MD)
- Patient Advocate SC (Co-Chairs: Susan Leigh, RN & Jim Williams, MS)
- Timeline calls for completion of SSC transition by 2010; hematologic malignancies next

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GI Steering Committee Activities: March 2006 - November 2008

- Evaluated 15 concepts; 8 approved, and 6 disapproved
  - Disease sites (pancreas, colon, esophagus, hepatocellular, rectal, neuroendocrine, GIST)
  - Therapeutic modalities included chemotherapy, VEGF inhibitors, EGFR inhibitors, radiation, & chemoembolization
- Regular face-to-face meetings at ASCO & GI ASCO
- Pancreas cancer State of the Science meeting December 2007: Consensus manuscript submitted
- Hepatocellular Task Force Clinical Trials Planning Meeting December 12-13, 2008

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GYN Steering Committee Activities: September 2006 – November 2008

- Committee reviews all phase 3 and randomized phase 2b concepts and randomized phase 2 concepts involving intergroup and international collaborations
- Fourteen (14) phase 3 concepts evaluated to date
- Seven (7) phase 2 concepts evaluated to date
- Fifteen (15) concepts approved (71%)
- Six (6) concepts Disapproved/Pending (29%)
- Cervical Cancer State of the Science meeting September 27-28, 2007, Bethesda MD
- In planning – Joint GCSC/Symptom Management and Health, 2009
- In planning – New trial development for treatment of women with advanced ovarian cancer, 2009

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SxQOL SC: Responsibilities

- Prioritize concepts for symptom management trials and trials to improve health quality of life
- Convene Clinical Trial Planning meetings to identify critical questions to prioritize strategies for NCI supported clinical trials
- Provide expertise in patient reported outcome measures and symptom control to Disease-specific Steering Committees

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SxQOL SC: Activities

- Reviewed 14 concepts: 3 approved, 6 needed revision, and 5 disapproved
  - Symptoms include peripheral neuropathy, chemotherapy rash, nausea and vomiting, radiation dermatitis, weight loss, fatigue, hot flashes, and vaginal stenosis
- Developed prioritization criteria for integral symptom management and quality of life studies
- Chemotherapy-Induced Peripheral Neuropathy Clinical Trials Planning Meeting – March 23, 2009

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Biomarkers, Imaging and QOL Studies

- Developed mechanism to support Coop Groups and CCOP Research bases so that critical biomarker and quality of life studies integral to national phase III clinical trials could be pursued: $5M in 2008
- Developed assay standardization criteria for use in prioritization of requests for these funds
- Developed evaluation criteria for prioritization of essential symptom management and quality of life studies

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Prioritization: Integral and Integrated Studies

1. *Integral* studies: a test that must be performed in order for the trial to proceed
   - Test to establish patient eligibility
   - Test for patient stratification
   - Test to assign patient to treatment arm, including early response endpoints for assignment of treatment during a trial

2. *Integrated* studies: studies that are intended to identify or validate markers and imaging tests or QOL instruments that might be used in future trials
   - Study plans clearly described in trial protocol
   - Tests performed on all cases although results not used to guide decisions in current trial

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BIQSFP: Eligible Trials 2008

- Essential biomarker, imaging, and QOL studies associated with:
  - Cooperative Group Studies
    - Phase 3 Treatment
    - Phase 3 Prevention
  - Symptom Management Studies

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2008 BIQSFP Supported Applications

- *COG: Phase III Randomized Trial of Gemtuzumab Combined with Conventional Chemotherapy for De Novo Acute Myeloid Leukemia (AML) in Children, Adolescents, and Young Adults*
- *NSABP: Biobehavioral Mechanisms of Fatigue in Patients Treated on NSABP-B-45*
- *GOG: Validation of PROMIS Tool For Fatigue in Conjunction with Treatment for Endometrial CA*

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CTWG Restructuring Initiatives

- Enterprise-Wide/Integrated Management
- Prioritization/Scientific Quality
- Coordination

  Coordinate clinical trials research through data sharing and providing incentives for collaboration
- Standardization
- Operational Efficiency

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Coordination Initiatives: Progress

- Developing a comprehensive database of NCI-supported clinical trials
- Developing mechanism to support multi-site translational clinical trials in rare diseases and areas not currently a major focus for Coop Groups
  - Pilot studies from H&N SSC and H&N SPORES initial focus utilizing the NCI's CTSU
- Guideline harmonization and incentives for collaboration across NCI clinical trials mechanisms: CCSG, SPORE, and Cooperative Groups

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Clinical Trials Reporting Program (CTRP)

- Operational Pilot began July 7, 2008
- Pilot sites:
  - Dana-Farber
  - Northwestern
  - Mayo
  - St. Jude
  - Wake Forest
- Production system for trial registration an abstraction “went live” January 5, 2009

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Staged Deployment of CTRP

- Interventional trials only for 2009
- First Quarter of 2009: five pilot sites only, new trials only, no amendments
- Second Quarter of 2009: solicited “early adopter” Cancer Centers begin entering new trials, allow amendments, allow existing trials
- Third Quarter of 2009 (provisional): all Cancer Centers begin entering new trials
- Fourth Quarter of 2009 (provisional): add Non-Cancer Center grantees & begin entering new trials, begin collection of accrual data
- First Quarter of 2010 (provisional): begin pilot reporting of outcomes, adverse events

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Clinical Trials Database (www.cancer.gov/ncictrp)

NCI's Clinical Trials Reporting Program

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Questions about cancer?

- 1-800-4-CANCER
- LiveHelp® online chat

NCI Highlights

Treatment of Metastatic Breast Cancer
Long-Term Smoking Cessation Cuts Risk

NCI is establishing a new Clinical Trials Reporting Program (NCI CTRP), based on a June 2005 recommendation submitted by the Clinical Trials Working Group (CTWG), which was approved by the National Cancer Advisory Board.

Even though NCI grantees are currently subject to trial reporting requirements, an upgraded set of mandatory reporting requirements will apply starting January 2009. In the long-term, the new reporting measures will help provide critical data to assist NCI in better coordinating research efforts to optimize our nation's investment in cancer research.

NCI clinical trials reporting will include up-to-date information about the status of all NCI-funded and/or sponsored clinical research, regardless of drug development phase, type of intervention or treatment, study design, or program through which funding is provided.

For More Information

NCI's Clinical Trials Reporting Program
Frequently Asked Questions
Background

Timeline

January 1 - June 30, 2009
All open trials to be registered

October 31, 2009
First submission deadline for accruals and updates

2008 2009 2010 2011

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Coordination Initiatives: Integration of NCI's Clinical Trials System

CTAC Coordination Subcommittee:
James Abbruzzese, MD Chair

Collaboration across NCI clinical trials mechanisms: Cancer Centers, SPOREs, and Cooperative Groups

- Harmonize guidelines; refocus review
- Remove disincentives to collaboration
- Develop new incentives for appropriate hand-offs
- Report to CTAC 3/09

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CTWG Restructuring Initiatives

- Enterprise-Wide/Integrated Management
- Prioritization/Scientific Quality
- Coordination
- Standardization

  Standardize informatics infrastructure and clinical research tools
- Operational Efficiency

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Standardization Initiatives: Progress

- Remote data capture system for Coop Group trials: Distribute to all NCI-supported Clinical Trials Sites
- eCRF Initiative
- Standard Clinical Trials Agreement Clauses

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Standardized Clauses

- Final negotiated agreements showed greater than 67% convergence on the vast majority of concepts analyzed
- Drafted proposed clauses based on common concepts identified
- Obtained input on proposed clauses from legal and business participants
- Refined proposed clauses based on feedback
- Obtained favorable Business Review Letter from Dept. of Justice 9/17/08: Project reviewed; no intention to challenge initiative

http://cancercenters.cancer.gov

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Standardization Initiatives: Progress

- Remote data capture system for Coop Group trials: Distribute to all NCI-supported Clinical Trials Sites
- eCRF Initiative
- Standard Clinical Trials Agreement Clauses
- Decrease reporting requirements (data elements) needed for Cooperative Group/Pharma trials used for secondary NDA's, including imaging for PFS

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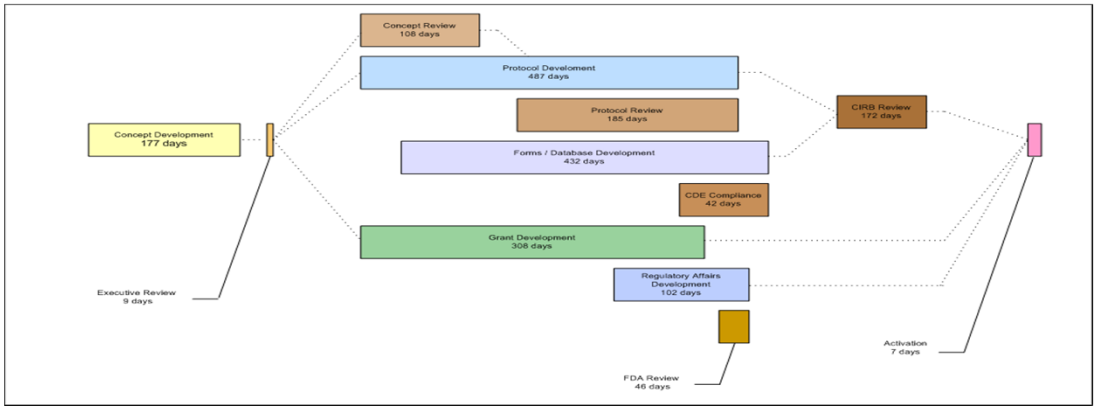
Operational Efficiency: Progress

- Developed clinical trial complexity models: provided additional support for rapid completion of difficult phase III studies
- Provided supplements to Minority-Based CCOPs and other infrastructures to enhance minority and underserved patient accrual
- Completed management analysis of clinical trials activation timelines at Coop Groups, Cancer Centers, and CTEP
- CTAC Operational Efficiency Working Group charged to develop approach to major operational change to enhance timeliness

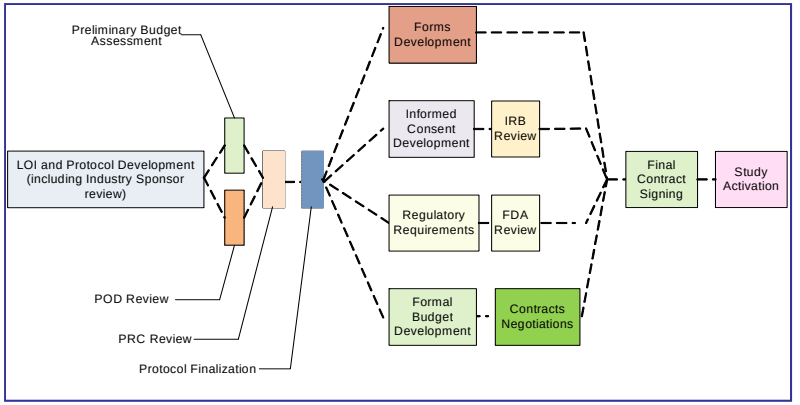
Opening a Cooperative Group Study

Cooperative Group Processes



Median: 784 to 808 days*
Range: 435-1604 days

Comprehensive Cancer Center Processes



Median: 116 to 252 days*
Range: 21-836 days

* Depending Upon Site, based on the Phase III trials studied

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Clinical Trials Advisory Committee Charge

The Clinical Trials Advisory Committee (CTAC) Charge:

Establish a CTAC Operational Efficiency Working Group (OEWG) to recommend strategies for reducing the time for activation of NCI-supported clinical trials.

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OEWG Highlights

- **The OEWG - constituted**
  - ~ 62 members
    - Chair: Gabriel Hortobagyi, MD
    - Co-Chair: James Doroshow, MD
- **Orientation Teleconferences** (5)–10-11/08
  - Scope (type of trials)
  - Components of trial activation
  - Obstacles to trial activation
- **OEWG Face-to-Face Meeting** – 12/19/08

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OEWG Membership

- **62 clinical trial stakeholder representatives**
  - Cancer Centers – leadership and protocol/trial specialists
  - Cooperative Groups – leadership and protocol/trial specialists
  - Pharma/Biotech
  - FDA
  - CMS
  - Patient Advocates
  - Community Oncologists
  - Statisticians
  - Patient Advocates
  - NCI – DCTD, DCP, CCR, & OD

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OEWG Mission

- Phase I: Develop strategies and implementation tactics for reducing the time for initiation of Cooperative Group and Cancer Center trials
  - Reduce study activation time by at least 50%
  - Optimize NCI, sponsor, and investigator interactions to reduce delays
- Phase II: Develop strategies and implementation tactics for reducing the time for completion of Cooperative Group and Cancer Center trials
  - Increase the percentage of studies successful in reaching accrual target
  - Assure timely completion of studies

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OEWG Trial Activation Situations

1. Cooperative Group Phase II and III Trials
2. Cooperative Group Investigational Drug Branch (IDB) Trials
3. Cancer Centers – Investigator-Initiated Trials
4. Cancer Centers – Cooperative Group Phase II and Phase III Trials
5. Cancer Centers – Investigational Drug Branch (IDB) Trials

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OEWG Progress

For Cancer Centers and Cooperative Groups there is:

- Agreement on the components of the trial activation process to be examined
- Agreement that timelines for opening all of the clinical trial types must be reduced by at least 50%
- Agreement on existing barriers to speedy trial activation
- Agreement that to substantively improve trial activation timelines will require major changes in every component of the system

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OEWG: Next Steps

- Analyze potential solutions identified at the OEWG December meeting and refine target timelines
- Develop draft recommendations to address barriers and reduce time to activation
- Plan next OEWG meeting to:
  - Prioritize recommendations
  - and identify implementation strategies
- Develop implementation plans for prioritized recommendations

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The NCI Translational Research Working Group (TRWG)

TRWG:

Implementation Update

Lynn Matrisian, Ph.D.
Sheila Prindiville, M.D., M.P.H.

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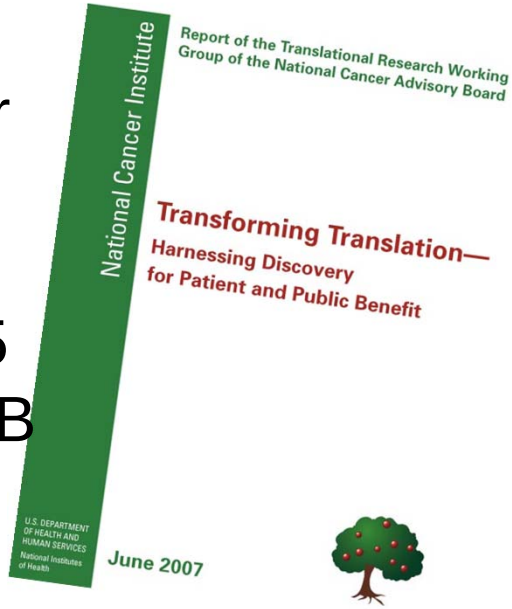
The NCI Translational Research Working Group (TRWG)

- 63 scientists, clinicians, advocates, and thought leaders from academia, government, and industry

- Charged to evaluate the current status of NCI's investment in translational research & envision its future in an inclusive, representative & transparent manner

- Produced a 150 page report with 15 recommendations accepted by NCAB June 2007: www.cancer.gov/trwg



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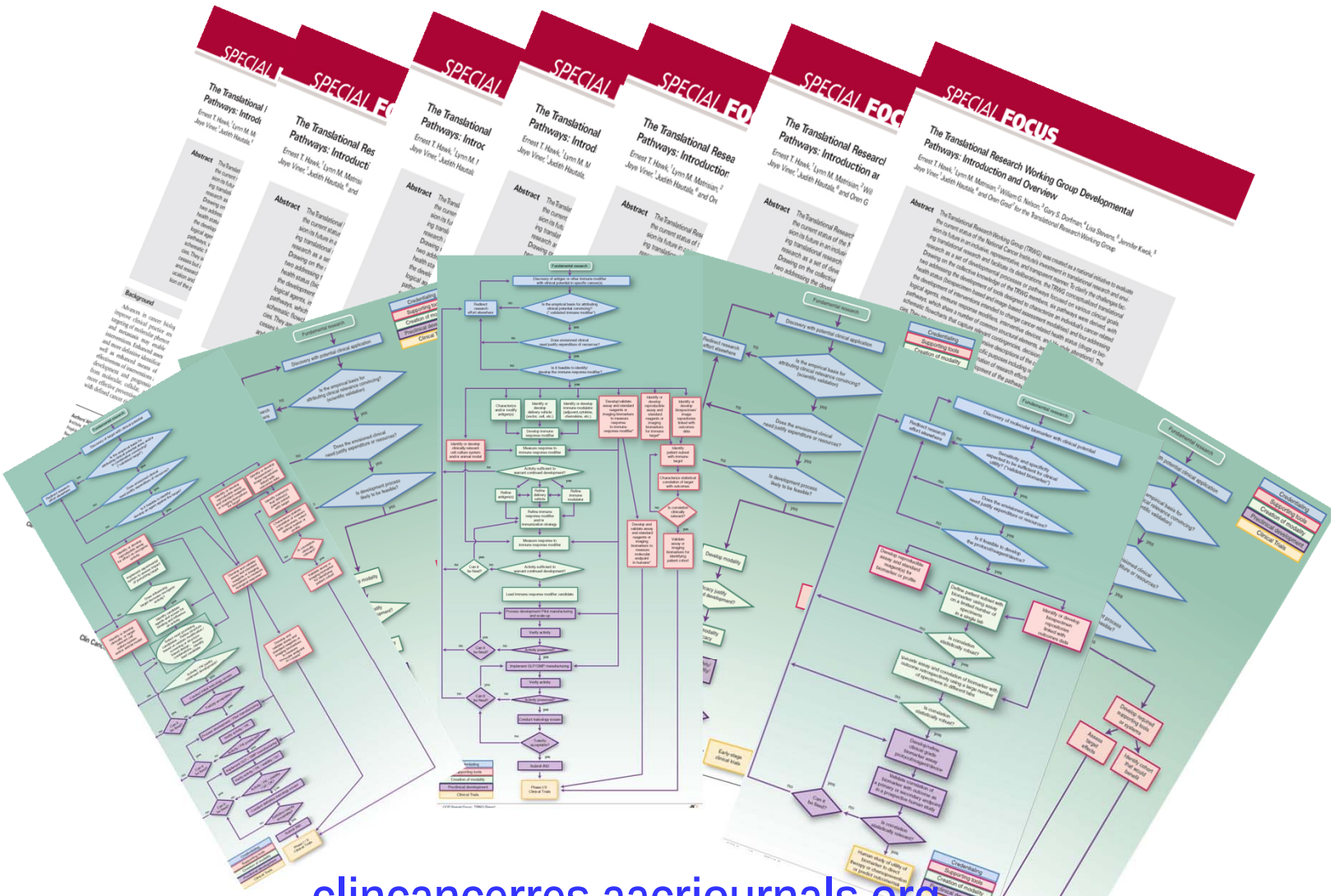
TRWG Pathways to Clinical Goals



clincancerres.aacrjournals.org

CCR 14: 5663-5713 (2008)

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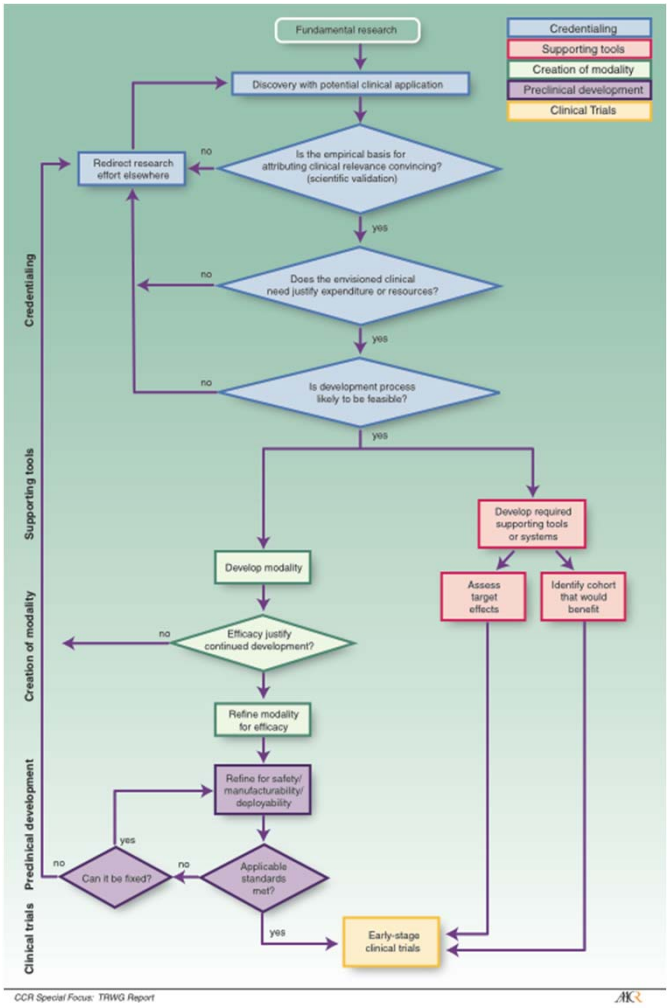
The Challenge of Early Translation



How can we best assure that:

- The most promising concepts enter the developmental pathways?
- Concepts that do enter advance to the clinic or to productive failure?
- Progress is as rapid, efficient and effective as possible?

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Translational Research Acceleration Initiative

Select several projects/year that are "ripe" for translation

- **Translational Research Acceleration Process Will:**
  - Gather information on translational opportunities
  - Prioritize translational research opportunities
  - Develop a funding & project management plan to accelerate prioritized opportunities

- **Translational Research Acceleration Process Will NOT:**
  - Impact Discovery research
  - Replace existing infrastructure or mechanisms for clinical or translational research

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STEP 1: Figure Out How to Gather Information

NCI Translates
NCI-wide Translational Science Meeting

- November 7-9, 2008, Washington, DC
- Coordinating Center for Clinical Trials
  - Sheila Prindiville, M.D., M.P.H.
  - Lynn Matrisian, Ph.D.
- 513 abstracts
  - Grants/PIs selected by NCI Program Staff
- 800 invited participants
  - NCI-funded scientists/clinicians
  - Advocates
  - NCI staff

http://ncitranslates.nci.nih.gov

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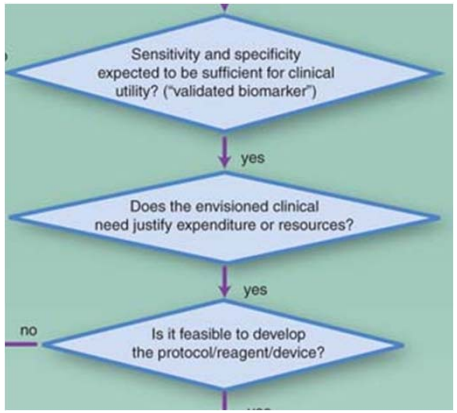
Translational Research Opportunity

- Focuses on a ***clinical goal***
  - Develops a modality (drug, device, biomarker, etc) that can be tested in people
  - Identifies the population/cancer type in which it is tested
- Describes ***scientific validity***
- Details ***clinical need***
- Provides information on ***feasibility***
  - Identifies individuals/research groups with projects or capabilities relevant to pathway domains



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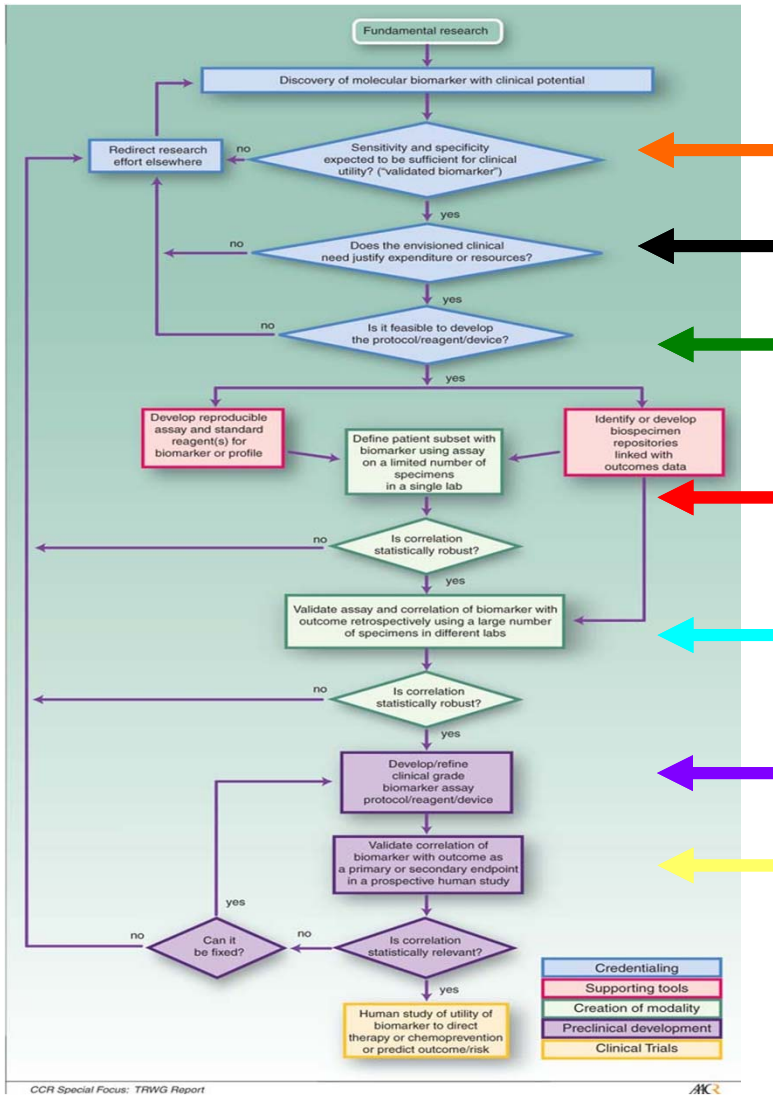
Translational Research Opportunities



Examples:

- Presented at Translational Science Meeting by Poster Discussion Session Co-chairs based on session abstracts
- Educated how abstracts could coalesce into a translational research opportunity
- Not prioritized

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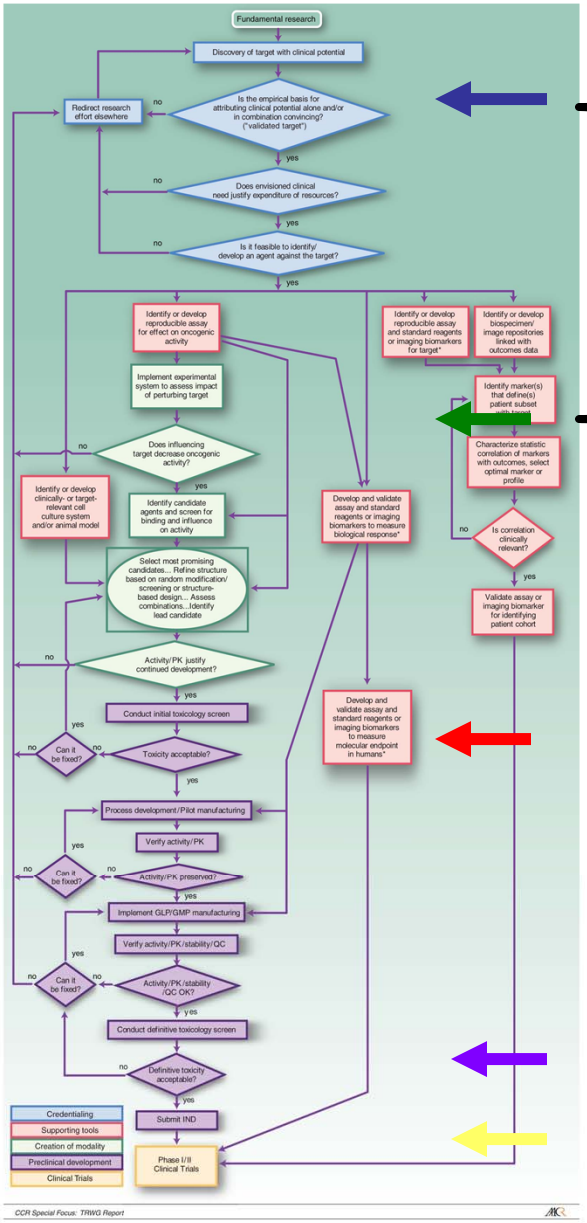
Agents: Targeting the Wnt Pathway



- Stem cell regulatory network
- Extensive evidence for causal role in CRC and others

- VU-WS30 (anti-helminth) identified in Xenopus egg assay to block Axin degradation & prevent Wnt signaling
- Modifications required to overcome limited systemic access

- Inhibits β-catenin induced proliferation of colon cancer cell lines
- Mouse models of CRC available
- Assays for Wnt signaling needed

- Tox, etc, needed on modified agent
- CRC for initial trials

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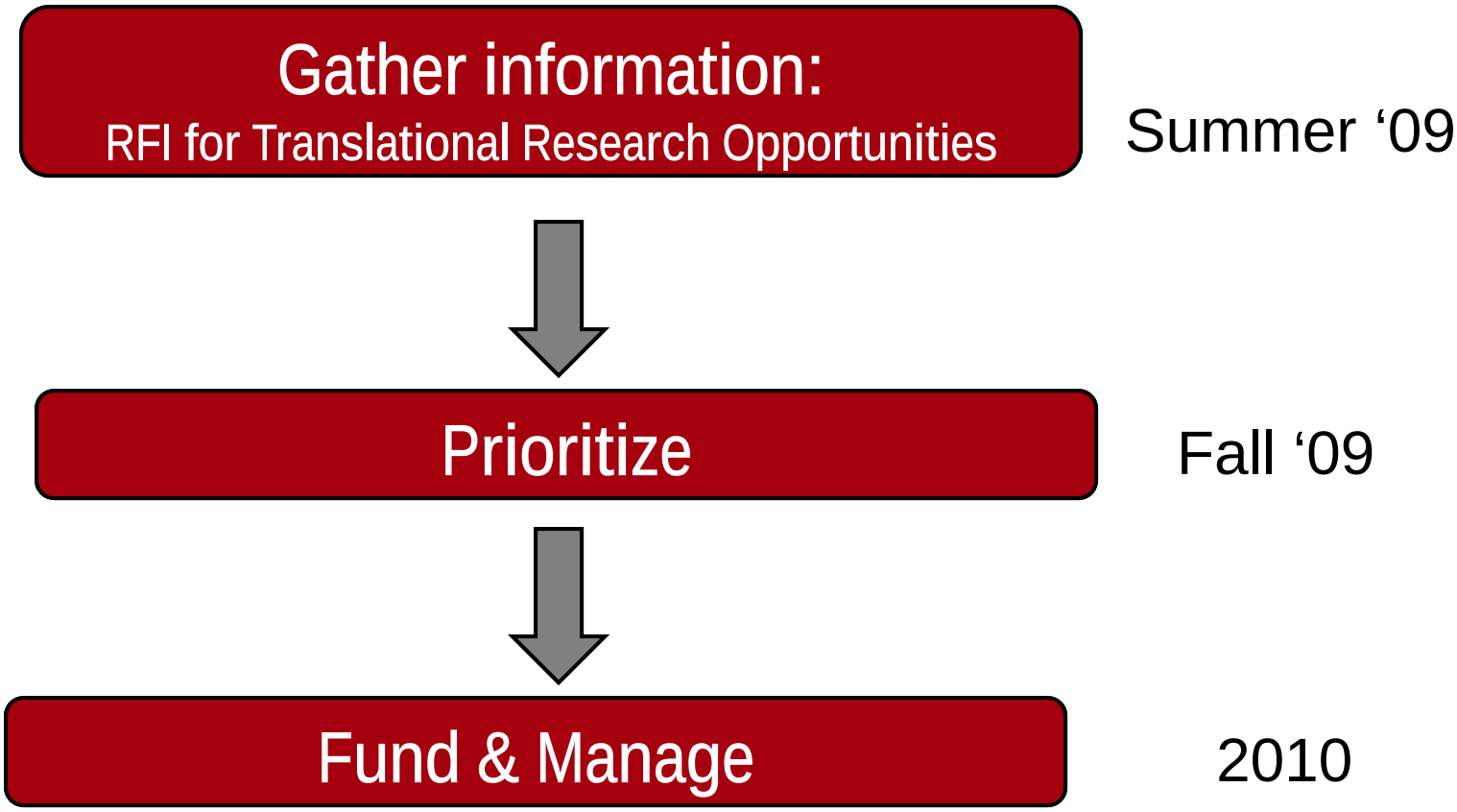
What Next?

CTAC recommended that NCI proceed with establishing a process to accelerate translational cancer research (Dec 08):



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Critical Elements for a Process to Prioritize Translational Research Opportunities

Intra-pathway Prioritization

Pathway-specific criteria determined and weighted; prioritization performed by extramural content experts

Inter-pathway Prioritization

Performed by the Clinical and Translational Research Advisory Committee (CTAC) of the NCI

Executive Decisions

NCI leadership

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Proposed Funding Strategy

Special Translational Research Acceleration Project (STRAP)

- Requirements:
  - Goal of completing early stage human studies
  - Project management plan
  - Specific development milestones and timelines
  - Development/commercialization strategy
- Funds for new and/or expanded projects
- Project management would link new or existing teams and projects and facilitate hand-offs between groups
- Opportunities to include industry/foundation funding or participation

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Approach to Project Acceleration

NCI Challenges

- Develop Project Management capabilities
  - Required to link new or existing teams/projects and to facilitate hand-offs between groups
- Develop customized funding strategies
  - Funding mechanisms and sources depend on project specifics
  - Range from expansion of existing activities to new activities
  - Require extraordinary coordination

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Approach to Project Acceleration

Extramural Challenges

- New institutional intellectual property strategies for collaborative research required
- New collaborative work flow models required
- New data sharing models required

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Approach to Project Acceleration

NCI and Extramural Joint Challenges

- Develop milestones and timelines that factor in consequences and contingencies
- Develop commercialization strategies
- Explore opportunities that include industry and/or foundation participation

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TRWG Implementation
Next steps & Timeline

Gather information:
RFI for Translational Research Opportunities — Late summer ‘09

↓

Prioritize — Fall ‘09

↓

Fund & Manage — 2010

NCI Clinical/Translational Research Management
Implementation of CTWG/TRWG Initiatives